In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 15-235V

Filed: November 14, 2019

KRISTEN SILVERIO, *on behalf of her minor child,* G.L.,	*	To Be Published
Petitioner,	*	Varicella Vaccine; Pneumococcal Conjugate Vaccine; Febrile seizures; Intractable Epilepsy; Entitlement to Compensation
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Andrew D. Downing, Esq., Van Cott & Talamante, PLLC., Phoenix, AZ, for petitioner.
Daniel A. Principato, Esq., U.S. Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

Roth, Special Master:

On March 6, 2015, Kristen Silverio ("petitioner") filed a petition on behalf of her minor child, G.L., pursuant to the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10 *et seq.*[2] ("Vaccine Act" or "the Program"). Petitioner alleges that G.L. had an adverse reaction to varicella and pneumococcal conjugate vaccinations received on April 16, 2012. *See* Petition, ECF No. 1. According to petitioner, the morning after G.L. received the subject vaccinations, she

[1]This Ruling has been designated "to be published," which means I am directing it to be posted on the Court of Federal Claims's website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (codified as amended at 44 U.S.C. § 3501 note (2006)). **This means the Ruling will be available to anyone with access to the internet.** However, the parties may object to the Ruling's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the whole Ruling will be available to the public. *Id.*

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755 (1986). Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

experienced a fever, which in turn caused a complex febrile seizure and subsequent epileptic seizures and disorders. *See* Petition, ECF No. 1.

After carefully analyzing and weighing the evidence presented in this case in accordance with the applicable legal standards, I find that petitioner has provided preponderant evidence that G.L.'s intractable epilepsy was caused and/or triggered by the vaccinations she received on April 16, 2012. Respondent has failed to rebut that showing with sufficient evidence of an alternative cause. The case shall accordingly proceed to damages.

I. Issues to be Determined

The parties have stipulated to the following facts: G.L. was born a healthy baby girl on April 10, 2011; prior to receiving varicella and pneumococcal vaccinations on April 16, 2012, G.L. had no clinical manifestations of neurological issues; G.L. had a complex febrile seizure on April 17, 2012; G.L. had two seizures on May 3, 2012 and was diagnosed with complex febrile seizure disorder; G.L. received a measles-mumps-rubella ("MMR") vaccination July 17, 2012; G.L. experienced another complex febrile seizure on July 23, 2012; G.L. experienced subsequent seizures on December 25, 2012, January 4, 2013, January 14, 2013, August 6, 2013, and December 14, 2014; G.L. has been diagnosed with intractable epilepsy; and G.L. has suffered from sequelae of her seizure disorder in excess of six months from the date that she received the allegedly causal vaccinations. Joint Submission ("Jt. Sub.") at 1-2, ECF No. 60.

The parties disagree on the following issues, which must be determined within this Ruling: (1) whether G.L.'s April 17, 2012 seizure was caused by her April 16, 2012 vaccinations; (2) whether there is a medical theory causally connecting G.L.'s vaccinations to her epilepsy; (3) whether there is a logical sequence of cause and effect showing that G.L.'s vaccinations were either the reason for, or a significant contributing factor to, her development of epilepsy; (4) whether there is a proximate temporal relationship between G.L.'s vaccinations, her complex febrile seizures, and her epilepsy; and (5) whether G.L.'s epilepsy was caused by factors unrelated to her vaccination. Jt. Sub. at 2.

II. Background

A. Procedural History

Petitioner filed her petition on March 6, 2015. ECF No. 1. This matter was initially assigned to Special Master Dorsey but reassigned to me on October 21, 2015. *See* ECF Nos. 4, 24. Petitioner filed medical records through November of 2015. Petitioner's Exhibits ("Pet. Ex.") 1-7, ECF No. 6; Pet. Ex. 8, ECF No. 8; Pet. Ex. 9, ECF No. 12; Pet. Ex. 10, ECF No. 13; Pet. Ex. 11, ECF No. 16; Pet. Ex. 12, ECF No. 22; Pet. Ex. 13, ECF No. 28; Statement of Completion, ECF No. 29.

On February 8, 2016, respondent filed a Rule 4(c) Report ("Rule 4") stating that compensation was not appropriate. ECF No. 34.

On June 8, 2016, petitioner filed an expert report and CV from Dr. David Siegler. Pet. Ex. 15-16, ECF No. 37. Petitioner filed additional medical records in September of 2016. Pet. Ex. 25, ECF No. 41; Pet. Ex. 26, ECF No. 42.

On September 26, 2016, respondent filed an expert report and CV from Dr. Gregory Holmes. Resp. Ex. A-B, ECF No. 44.

A status conference was held on October 26, 2016. The parties agreed to schedule this matter for an entitlement hearing "with the hope that they [could] reach an informal resolution before then." Scheduling Order at 1, ECF No. 47.

A prehearing order was issued on December 13, 2016, setting this matter for an entitlement hearing on April 18 and 19, 2018, in Washington, DC. Prehearing Order, ECF No. 49.

Respondent filed medical literature on October 13, 2017. Resp. Ex. A, Tabs 1-10, ECF No. 51; Resp. Ex. A, Tabs 11-16, ECF No. 52.

Petitioner filed her pre-hearing brief ("Pet. Brief") and medical literature on February 21, 2018. Pet. Ex. 17-28, ECF No. 55; Pet. Brief, ECF No. 56. Respondent filed his pre-hearing brief ("Resp. Brief") on March 14, 2018. Resp. Brief, ECF No. 58. Petitioner filed a reply brief on March 27, 2018. ECF No. 59. The parties' joint submission was filed on April 4, 2018. ECF No. 60.

In April of 2018, petitioner filed additional medical literature, additional genetic testing results, an updated CV for Dr. Siegler, and supplemental medical records. Pet. Ex. 29-30, ECF No. 64; Pet. Ex. 31, ECF No. 67; Pet. Ex. 32-33, ECF No. 68.

An entitlement hearing was held in Washington, DC on April 18, 2018. Scheduling Order at 1, ECF No. 69. At the end of the hearing, petitioner requested the opportunity to further address Dr. Holmes's opinion that a fever cannot cause frontal lobe seizures, the type of seizure that G.L. suffered. *Id*. Petitioner was ordered to file a supplemental report from Dr. Siegler addressing the testimony offered by Dr. Holmes at hearing. *Id*.

Petitioner filed a supplemental report from Dr. Siegler on May 30, 2018 and supporting medical literature on June 1, 2018. Pet. Ex. 34, ECF No. 73; Pet. Ex. 35-43, ECF No. 75.

Petitioner filed a statement from Wesley Lisee, the husband of petitioner and father of G.L., on July 9, 2018. Pet. Ex. 44, ECF No. 81.

Respondent filed a responsive report from Dr. Holmes on July 16, 2018 and supporting medical literature on July 25, 2018. Resp. Ex. C, ECF No. 82; Resp. Ex. C, Tabs 1-10, ECF No. 83; Resp. Ex. C, Tabs 11-20, ECF No. 84; Resp. Ex. C, Tabs 21-30, ECF No. 85; Resp. Ex. C, Tabs 31-35, ECF No. 86.

The parties filed post-hearing briefs on October 15, 2018. *See* ECF Nos. 87-88.

This matter is now ripe for decision.

B. Summary of Medical History[3]

Though G.L. had some issues with low birth weight and failure to thrive initially, G.L.'s medical history prior to April of 2012 is not raised as an issue in this case. *See generally* Pet. Ex. 2-4. She received all of her vaccinations during her first year of life without event. Pet. Ex. 2 at 1; Pet. Ex. 3 at 4; Pet. Ex. 4 at 101, 103-04. G.L. had normal childhood illnesses with fevers with no untoward events. She did not have any seizures.

On April 16, 2012, G.L. was seen by Dr. Kurker for a well child one-year old checkup. Pet. Ex. 4 at 95. She had a normal exam and there were no concerns. *Id*. G.L. received her fourth pneumococcal and first varicella vaccinations. *Id*.; Pet. Ex. 2 at 1.

1. G.L.'s First Set of Seizures – April 17, 2012

On the morning of April 17, 2012, petitioner heard a strange noise and found G.L. in her crib, seizing. Pet. Ex. 2 at 4; Pet. Ex. 6 at 4. Petitioner called 911. *Id*. Upon arrival, EMS noted generalized seizure activity. Pet. Ex. 6 at 4. Ativan[4] was administered intramuscularly and G.L.'s seizure activity stopped. *Id*. Upon arriving at the emergency room ("ER") at Connecticut Children's Medical Center ("CCMC"), G.L. began having seizure activity again, affecting only her left side. *Id*. Both EMS and ER personnel noted that G.L. had received vaccinations the day before. *Id*.; Pet. Ex. 2 at 4; Pet. Ex. 5 at 107. The ER record states that G.L. had a tonic-clonic seizure lasting longer than 15 minutes which was associated with a fever of 102[5] and was somnolent with respiratory distress. Pet. Ex. 2 at 4-5, Pet. Ex. 5 at 107. She was noted to have decreased tone and weakness in her left arm and leg and tachycardia. Pet. Ex. 2 at 5; Pet. Ex. 5 at 108. While seizing, she had focalized tonic-clonic movement in her left arm and leg and a right gaze preference. *Id*. Petitioner reported to both EMS and ER personnel that G.L. was well the night before but was warm to the touch that morning. Pet. Ex. 6 at 4; Pet. Ex. 5 at 107.

G.L.'s treating physicians noted that her seizures "could be secondary to infection," and a head CT, lumbar puncture, blood culture, and urinalysis were performed. Pet. Ex. 5 at 119, 141. The head CT was normal and the lumbar puncture results were "not concerning for infection." *Id*. The "CBC[6] did show a very elevated [white blood cell] count of 33.9 but with no left shift + no focus of infection, this may just be a stress response + do not plan to [treat with antibiotics] at this time." *Id*. at 123. It was noted that "[t]he fact that she received vaccines yesterday make it more

[3] This medical summary contains the facts most relevant to the disposition of this case. However, I considered the record as a whole. A more detailed summary of the facts may be found in respondent's Rule 4(c) Report and in the parties' respective briefs.

[4] Ativan is the brand name for lorazepam, a medication with sedative effects used to control status epilepticus. *Ativan*, DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 173 (32d ed. 2012) [hereinafter DORLAND'S]; *lorazepam*, *id*. at 1074.

[5] Other records from CCMC state that G.L. had a fever of 104. *See* Pet. Ex. 5 at 121, 140.

[6] CBC, or complete blood cell count, is a series of tests that measure levels of different types of blood cells. *See Mosby's Manual of Diagnostic and Laboratory Tests* 156-57 (Pagana eds., 6th ed. 2018) [hereinafter *Mosby's*].

likely that the fever is related to the vaccines, especially since pneumovax + Varivax have both been associated [with] febrile seizures." *Id*. The plan was to repeat the CBC the next morning and to observe G.L. for development of new symptoms to indicate a source of fever. *Id*.

A repeat CBC was performed on April 18, 2012, and G.L.'s white blood cell count was normal at 15.6, "likely elevated yesterday secondary to stress response of seizures." Pet. Ex. 5 at 141. It was noted that her seizure "could be due to getting vaccines prior to episode." *Id*. G.L. was afebrile and did not have any signs of infection. *Id*. An EEG[7] was performed and was "a normal awake and asleep EEG without any clear evidence of epileptiform discharges or focal slowing." *Id*. at 15; Pet. Ex. 11 at 141.

G.L. was discharged on April 19, 2012 with a principle diagnosis of complex febrile seizures. Pet. Ex. 5 at 127.

On April 20, 2012, G.L. was presented to the pediatrician for a follow-up for complex febrile seizures, status post-injections. Pet. Ex. 4 at 94. The pediatrician noted that G.L. had had a seizure which lasted for 30 minutes, but was doing better and was back to eating, drinking and urinating. *Id*. She was noted to have had a complex seizure which had resolved and was "most likely do (sic) to immunization." *Id*.

2. G.L.'s Second Set of Seizures – May 3, 2012

On May 3, 2012, G.L. was transported to the ER at CCMC via EMS with febrile seizure and viral illness. Pet. Ex. 3 at 22; Pet. Ex. 6 at 9. Petitioner reported that G.L. had been cranky and clingy that day and felt warm that afternoon. Pet. Ex. 3 at 22. Petitioner gave her ibuprofen; about two minutes later, G.L.'s eyes rolled back in her head and to the left, and she stopped breathing. *Id*. G.L. had a few tonic-clonic movements of her left arm and leg. *Id*. Her lips turned blue and her dad gave her rescue breaths. *Id*. The seizure resolved without medication after five minutes. *Id*. In the ER, G.L. was noted to have a fever of 103. *Id*. at 23. On discharge, petitioner was instructed to continue ibuprofen to prevent a temperature spike and to keep the MRI as scheduled. *Id*.

Later that day, around 7:30 pm, G.L. had another seizure. Pet. Ex. 5 at 37. EMS personnel arrived and administered oxygen. Pet. Ex. 6 at 14. Prior to transport, G.L. had another seizure that lasted over ten minutes without breaking. *Id*. Versed[8] was administered intramuscularly and the seizure stopped. *Id*. G.L. was transported to CCMC; when she arrived at the ER, she was still having seizure activity. Pet. Ex. 5 at 37. Ativan was administered. *Id*. G.L. did not return to baseline and was administered Keppra.[9] *Id*. She was admitted to the pediatric intensive care unit for "close

[7] An EEG, or electroencephalogram, is a graphic recording of the electrical activity of the brain. It is performed to identify and evaluate patients with seizures. *See Mosby's* at 490.

[8] Versed is the brand name for midazolam, a medication used as an antianxiety agent and muscle relaxant. It is similar to diazepam, but stronger. *Versed*, DORLAND'S at 2050; *midazolam, id*. at 1165.

[9] Keppra is the brand name for levetiracetam, an anticonvulsant medication used in the treatment of partial and myoclonic seizures and idiopathic generalized epilepsy. *Keppra*, DORLAND'S at 978; *levetiracetam, id*. at 1031.

neurologic and respiratory monitoring in the setting of status epilepticus." *Id*. She had tachycardia secondary to dehydration, with presumed upper respiratory infection. *Id*. G.L. was discharged on May 5, 2012 with prescriptions for Diastat[10] and Keppra, and instructions to make an appointment with Dr. Acsadi in six to eight weeks. *Id*. at 40.

On May 7, 2012, G.L. was seen by the pediatrician for follow-up. Pet. Ex. 4 at 93. She appeared well and was taking Keppra. *Id*. The pediatrician noted that on her second presentation to the ER on May 3, G.L. had a seizure that lasted longer than 45 minutes. *Id*. She was scheduled for an MRI on May 13 and was scheduled to see Dr. Acsadi, a neurologist, in six to eight weeks. *Id*.

An MRI of the brain with and without contrast was performed on May 18, 2012 and was "essentially normal…demonstrating no findings suggestive of mesial temporal sclerosis." Pet. Ex. 12 at 1.[11]

On July 9, 2012, G. L. was presented to Dr. Acsadi. Dr. Acsadi noted that G.L. had not had any seizures since starting Keppra but had had two episodes of "staring off" during low-grade fevers. Pet. Ex. 5 at 10. G.L. had a normal neurological exam and was developmentally on track. *Id*. at 10-11. Her medical history was unremarkable, and she did not have a family history of seizures. *Id*. at 10. Dr. Acsadi agreed with the diagnosis of complex febrile seizures and recommended that G.L. return for a follow-up visit in four to five months. *Id*. at 11.

3. The Third Seizure – July 23, 2012

On July 17, 2012, at her 15-month well baby visit, G.L. was noted to have complex seizures for which she was taking Keppra but was otherwise healthy. Pet. Ex. 4 at 91. She was administered her first MMR vaccine. *Id*.; Pet. Ex. 2 at 1.

Six days later, on July 23, 2012, petitioner found G.L. in bed seizing. Pet. Ex. 3 at 9. After about three minutes, petitioner administered Diastat, and the seizure resolved. *Id*. at 10. 911 was called; upon arrival of EMS, petitioner reported that the seizure stopped after Diastat, but G.L. was not responding. Pet. Ex. 6 at 21. G.L. was transported to CCMC, where she was evaluated for seizure activity related to fever with left-sided arm and leg movement and left-sided facial twitch. Pet. Ex. 3 at 10. Petitioner reported that G.L. had been fussy the day before with no clear source of fever, no upper respiratory infection, no apparent discomfort, and no rash. *Id*. It was noted that this was G.L.'s third complex partial seizure[12] with fever. *Id*. at 11. She was kept for observation

[10] Diastat is the brand name for diazepam, a medication with many uses, including anticonvulsant and antitremor agent. *Diastat*, DORLAND'S at 511; *diazepam*, *id*. at 512.

[11] "Mesial temporal sclerosis," also known as "hippocampal sclerosis," is a loss of neurons in the hippocampal region with gliosis. It is sometimes seen in epilepsy. *Mesial temporal sclerosis*, DORLAND'S at 1680; *hippocampal sclerosis*, *id*. at 1680.

[12] A partial seizure occurs due to a lesion in a specific, known area of the cerebral cortex. The term "partial seizure" is used interchangeably with "focal seizure." *Partial seizure*, DORLAND'S at 1688. A complex partial seizure is a partial seizure characterized by varying degrees of impairment of consciousness; the

and reassessment. *Id*. She did not have any further seizure activity during the observation period and was discharged with instructions to follow up with the pediatrician. *Id*.

The following day, July 24, 2012, G.L. was seen by her pediatrician for follow-up for a febrile seizure with a fever of 102. Pet. Ex. 4 at 90.

On October 10, 2012, G.L. presented for her 18-month-old well child checkup. Pet. Ex. 4 at 89. She had a history of seizures possibly associated with immunizations but was otherwise healthy and meeting all milestones. *Id*. A decision to continue vaccinating was made. *Id*. G.L. received diphtheria-tetanus-acellular pertussis ("DTaP"), haemophilus influenzae b ("Hib"), and inactivated poliovirus ("IPV") that day without event. *Id*.

4. The Fourth Seizure – January 4, 2013

On January 4, 2013, G.L. was presented to the pediatrician. Pet. Ex. 4 at 86. Petitioner reported that G.L. had had a seizure that day which lasted for six minutes. *Id*. G.L. was standing near the couch when her eyes glazed over; she became unresponsive and started turning blue. *Id*. The paramedics were called. *Id*. Police arrived and administered oxygen and G.L. returned to baseline. *Id*. Diastat was given. *Id*. Upon exam, G.L. was neurologically and physically responding to light and sound. *Id*. Petitioner was advised to increase Keppra, alternate Tylenol and Motrin, and to give G.L. warm baths. *Id*.

5. The Fifth Set of Seizures – January 14, 2013

On January 14, 2013, G.L. had another seizure. Petitioner called 911 and administered Diastat. Pet. Ex. 6 at 26. The paramedics responded; petitioner reported that while G.L.'s father was holding her, petitioner noticed that G.L. had a "blank stare" which lasted for about 10 minutes. *Id*. Petitioner reported that G.L. had been diagnosed with croup the week before and had experienced flu-like symptoms the previous weekend. *Id*. She had a seizure three days ago. *Id*. Her dosage of Keppra had recently been increased. *Id*. G.L. was noted to be responsive to verbal stimuli and became more alert and playful during transport to CCMC. *Id*.

Upon exam at CCMC, G.L. had a maculopapular rash on her trunk and lower extremities, diffuse lymphadenopathy affecting her cervical lymph nodes, and exudate on her soft palate and pharynx. Pet. Ex. 3 at 19. It was noted that her father was recovering from a febrile viral illness. *Id*. G.L.'s dosage of Keppra was increased. *Id*. at 20. She was discharged home in good condition with a diagnosis of pharyngitis and fever. *Id*. at 18.

On January 17, 2013, G.L. was presented to the neurology clinic for follow-up. Pet. Ex. 5 at 6. G.L. had had three seizures since her last appointment in July of 2012. *Id*. Her parents reported a change in the seizure characteristics; G.L. no longer had jerking or shaking but her eyes glazed over, and she was "more vacant." *Id*. An EEG was ordered. *Id*. at 7.

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person affect performs non-purposeful, repetitive movements which she may not remember. *Complex partial seizure, id*.

On February 5, 2013, G.L. underwent an EEG, which was "a normal awake and asleep EEG without any definite epileptiform activity." Pet. Ex. 3 at 17.

In the months that followed, G.L. continued to be a healthy child, developing normally. Pet. Ex. 4 at 83. She continued to follow-up with neurology. Pet. Ex. 5 at 2-3.

6. The Sixth Seizure – August 5, 2013

On August 6, 2013, G.L. was presented to the pediatrician. She had had a four-minute seizure the night before, with a fever of 101.7. Pet. Ex. 4 at 81. Petitioner was alternating Tylenol and Motrin for G.L.'s fever. *Id*. G.L. was diagnosed with pharyngitis and prescribed Pen V (sic) by suppository. *Id*. Petitioner was instructed to continue giving Motrin and Tylenol and to encourage fluids, rest, and cold compresses. *Id*.

On August 8, 2013, G.L. was examined by Brenda Cowan-Frautschy, a nurse practitioner in the CCMC Department of Neurology. Pet. Ex. 3 at 12; Pet. Ex. 11 at 4. It was noted that G.L. had a seizure two days prior to the visit which was dealt with appropriately using Diastat. *Id*. The seizure stopped within one minute; G.L. slept and returned to baseline. *Id*. She had a fever of 103.6 and the next day was diagnosed with tonsillitis by the pediatrician. *Id*. Her last seizure was in February. *Id*. Upon exam, G.L. was alert and had normal speech. Pet. Ex. 3 at 13; Pet. Ex. 11 at 4. Keppra and Diastat were continued. Pet. Ex. 3 at 14; Pet. Ex. 11 at 5.

G.L. had febrile seizures on December 14, 2013, December 25, 2013, and January 9, 2014. Pet. Ex. 4 at 30-31, 61-63; Pet. Ex. 6 at 31, 35; Pet. Ex. 11 at 11-13.

On February 24, 2014, G.L. was presented to Dr. Jennifer E. Maden Cohen at the CCMC Department of Neurology for seizure disorder. Pet. Ex. 4 at 54; Pet. Ex. 11 at 19. G.L.'s most recent seizure was several days before; petitioner questioned whether it was part of an allergic reaction due to a rash that G.L. developed prior to the seizure. Pet. Ex. 4 at 55; Pet. Ex. 11 at 20. G.L. was developing normally, although petitioner expressed concerns that G.L. had "obsessive qualities" because she needed certain items such as blocks to be placed in certain ways, otherwise she would have a tantrum. Pet. Ex. 4 at 56-57; Pet. Ex. 11 at 21. Petitioner also noted that G.L. seemed to have difficulty with loud noises. Pet. Ex. 4 at 57; Pet. Ex. 11 at 21. Dr. Cohen noted that the majority but not all of G.L.'s seizures were associated with illness and fever. Pet. Ex. 4 at 57; Pet. Ex. 11 at 22. G.L.'s seizures were "complex partial in nature" which was atypical for febrile seizures. G.L. had also had an episode of status epilepticus.[13] *Id*. In Dr. Cohen's opinion, "All of these factors make one think that it is unlikely that the correct diagnosis for these seizures is febrile seizures. . .." *Id*. A 24-hour video EEG was ordered. *Id*. Dr. Cohen noted that G.L.'s behavior issues may be related to the Keppra and recommended a vitamin B6 supplement to hopefully counteract the side effects. *Id*.

On February 27, 2014, G.L. underwent Battelle Developmental Inventory, Vision and Hearing Screening. Pet. Ex. 4 at 66-74. There was no concern for her hearing or vision. *Id*. at 69. Her developmental skills were all within normal range; G.L. was "very verbal," could carry on a

[13] Status epilepticus is a continuous series of generalized tonic-clonic seizures without return to consciousness. It is a life-threatening emergency. *Status epilepticus*, DORLAND'S at 1767.

conversation, and had good play and motor skills. *Id*. at 73-74. Nonetheless, she was eligible for intervention services due to "an established condition of poorly controlled seizures." *Id*. at 73. Petitioner chose not to pursue services at that time. *Id*. at 74.

On April 9, 2014, G.L. was presented to Dr. William David Graf at the Yale School of Medicine, Department of Pediatrics, Neurology. Pet. Ex. 4 at 48. Dr. Graf provided a recitation of G.L.'s medical history, noting that G.L. had had nine seizures in her lifetime, including one lasting approximately an hour and 45 minutes for which she was hospitalized in intensive care. *Id*. at 49. G.L. was noted to be having "significant personality and mood changes" associated with her medication, which was disrupting the family. *Id*. She also had sensitivity to sound, but it was not certain whether this too was a side effect of the medication. *Id*. Dr. Graf noted a question of whether G.L.'s immunizations were the trigger. *Id*. Otherwise, G.L.'s neurodevelopmental history was normal, except for the seizures and medication-related issues, there was no family history of neurological or neurodevelopmental disorders, and there were no environmental risk factors. *Id*. at 49-50. Her neurological examination was normal. *Id*. at 51. The plan was to slowly taper G.L. off of Keppra and use diazepam as a rescue medication. *Id*. at 49, 52. Petitioner was instructed to contact Dr. Graf if G.L. continued to have seizures with and without fever. *Id*. at 52.

7. Subsequent Treatment and Development of Seizures without Fever

On April 22, 2014, G.L. was presented to CCMC for evaluation of petit-mal/absence seizures. Pet. Ex. 4 at 28. Petitioner reported that G.L. had a seizure that morning; after a few minutes, petitioner administered Diastat but G.L. needed a second dose in order for the seizure to stop. *Id*. G.L. had not had a recent illness or fever; petitioner reported that G.L. was fine when she awoke that morning. *Id*. Petitioner advised that Dr. Graf had recommended weaning G.L. off of Keppra because petitioner was concerned about G.L.'s behavior problems. *Id*. It was noted that G.L. apparently had a seizure without fever. *Id*. The plan was to temporarily increase G.L.'s dosage of Keppra and start her on Trileptal.[14] *Id*.

On May 20, 2014, G.L. returned to Dr. Cohen for "localization-related (focal)(partial) epilepsy and epileptic syndromes with complex partial seizures, without mention of intractable epilepsy." Pet. Ex. 11 at 29. G.L. was noted to be a three-year-old with "complex febrile seizures now likely generalized epilepsy" due to "two complex partial seizures outside of the setting of fever or illness." *Id*. at 36; Pet. Ex. 4 at 44. Her last seizure on May 10, 2014 was different than previous seizures because her head and eyes deviated to the right, while in past seizures it had deviated to the left. *Id*. The seizure lasted six minutes and stopped with Diastat. *Id*. G.L. was weaning off of Keppra and increasing Trileptal. *Id*. G.L.'s parents reported her throwing things and hitting and licking her sister while on Keppra; she could not be controlled. *Id*. G.L. was reported to be "an angel" when not on Keppra. *Id*. A 24-hour epileptic monitoring unit ("EMU") stay was scheduled for June 9, 2014. *Id*. Dr. Cohen noted that an MRI with and without contrast was performed on May 18, 2014 and was normal. Pet. Ex. 11 at 37; Pet. Ex. 4 at 45. Petitioner reported that G.L. was not having any difficulties in school but succeeding academically. Pet. Ex. 11 at 37; Pet. Ex. 4 at 46. G.L. had a normal exam. *Id*. The impression was generalized epilepsy.

[14] Trileptal is the brand name for oxcarbazepine, an anticonvulsant used in the treatment of partial seizures. *Trileptal*, DORLAND'S at 1967; *oxcarbazepine*, *id*. at 1355.

Pet. Ex. 11 at 38; Pet. Ex. 4 at 46. The plan was to continue weaning her off of Keppra and increasing Trileptal. *Id*.

On June 4, 2014, G.L. was presented to Dr. Acsadi for generalized seizures. Pet. Ex. 4 at 42; Pet. Ex. 11 at 44-45. Dr. Acsadi noted that G.L. had recently seen Dr. Cohen who suggested the possibility that Trileptal may have aggravated G.L.'s seizures. *Id*. There was a plan to switch G.L. to Topamax,[15] but petitioner had concerns since Keppra had caused behavioral problems. *Id*. Upon exam, G.L. had a slight upper respiratory infection but no fever, and her neurological exam did not suggest a focal deficit. Pet. Ex. 4 at 42-43; Pet. Ex. 11 at 45. An MRI from 2012 showed no findings suggestive of mesial temporal sclerosis. Pet. Ex. 4 at 43; Pet. Ex. 11 at 45. Dr. Acsadi's impression was convulsive and generalized seizures. *Id*.

On June 9, 2014, G.L. was admitted to CCMC for continuous video EEG monitoring. Pet. Ex. 4 at 22-23. She had 12 seizures in the past three months, with her most recent seizure on June 3, 2014. *Id*. at 22. She was being weaned off of Trileptal and had started Depakote[16] seven days ago. *Id*. Petitioner reported that G.L. had not had any seizures while on Depakote. *Id*. While at CCMC, G.L. was weaned off of Depakote in order to capture a seizure event. *Id*. at 23. Her baseline neurological status was partial epilepsy with complex partial seizures. *Id*. On the morning of June 13, 2014, G.L. had a 1-1.5-minute event with unresponsiveness, staring, and cyanosis; she desaturated to mid-60%, though not sustained. *Id*. at 24. Her seizure resolved without intervention and she was assisted with oxygen for 30 seconds. *Id*. She recovered without intervention and was stable on room air. *Id*. She was then loaded with Depakote after the EEG was reviewed and logged. *Id*. The plan was to continue weaning her off of Trileptal and continue with Depakote. *Id*. She was discharged that same day with a diagnosis of localization related focal partial epilepsy and epileptic syndromes with complex partial seizures, without mention of intractable epilepsy. *Id*. at 22.

On July 1, 2014, G.L. returned to Dr. Cohen, for review of the results of G.L.'s prolonged EEG monitoring. Pet. Ex. 11 at 48. According to Dr. Cohen, G.L.'s EEG was abnormal and "likely consistent with epileptogenicity from the right frontal region." Dr. Cohen further noted, "The seizure captured had a lead in from the right frontal region and throughout the recording[,] spikes were present over the right frontal region. It is possible that there is rapid spread from a right frontal focus to the bilateral frontal regions or in a generalized pattern, but it is possible that this represents a generalized epilepsy." *Id*. at 49. Dr. Cohen recommended further EEG monitoring. *Id*.

On July 9, 2014, G.L. presented to Dr. Ekaterina Bakradze, a neurologist at CCMC. Pet. Ex. 11 at 109; Pet. Ex. 4 at 40. G.L. had a seizure at the end of June which lasted longer than a typical episode. *Id*. G.L.'s family reported that she had been having seizures right after swimming in the pool. *Id*. G.L. usually had a seizure once per week; the seizures had different clinical presentations and durations, with the shortest being 50 seconds and occurring while she was in the hospital. *Id*. She was taking Trileptal and Depakote daily. *Id*. G.L. had a normal exam. Pet. Ex. 11 at 112, Pet. Ex. 4 at 41. She had intractable epilepsy and was continuing to have seizures despite

[15] Topamax is the brand name for topiramate, a medication used as an anticonvulsant in the treatment of partial seizures. *Topamax*, DORLAND'S at 1939; *topiramate, id*. at 1940.

[16] Depakote is the brand name for divalproex sodium, a medication used in the treatment of epileptic seizures, particularly absence seizures. *Depakote*, DORLAND'S at 490; *divalproex sodium, id*. at 558.

multiple mediation therapies. *Id*. Dr. Bakradze recommended a 3 Tesla MRI to look for subtle cortical dysplasia at the right frontal area and a PET scan[17] to look for hypometabolism at the right frontal area, which could suggest dysfunction in a corresponding area. *Id*. If they could find any focal structural abnormality that correlated with the focus of seizure onset, G.L. could benefit from surgery. *Id*. Dr. Bakradze also recommended a consultation at Yale or Boston Children's. *Id*.

G.L. continued to have seizures every few weeks; at times, she would exhibit a hand tremor when reaching for objects or doing a puzzle. Pet. Ex. 11 at 121. Her parents noted "spaciness" if G.L. did not eat for several hours. *Id*. They also noticed that during previous seizures, G.L.'s eyes went to the left, but in recent seizures, her eyes went to the right. *Id*. Her dose of Trileptal was increased but caused behavioral problems. *Id*. A work up for focal epilepsy was being pursued but the presence of left and right seizure manifestations caused concern that G.L. would not be a good candidate for epilepsy surgery. *Id*. at 122. Lamictal[18] was added to her drug regimen. *Id*.

On November 7, 2014, G.L was admitted to New York Presbyterian for 10 days for intractable focal epilepsy. Pet. Ex. 7 at 17. Her last seizure was a month ago. *Id*. She was presented for surgical workup, including ictal and interictal SPECT. *Id*. at 18. Brain perfusion scintigraphy was performed on November 11, 2014 and showed "[d]ecreased perfusion in the right frontal lobe which may represent an interictal epileptogenic focus." *Id*. at 55. Continuous EEG video monitoring was also performed. *See id*. at 55-57. During monitoring, G.L. had one complex partial seizure with secondary generalization correlated with staring and behavioral arrest, followed by generalized shaking with electrographic seizure onset arising from the frontal region, likely right front onset. *Id*. at 57. Diffuse background slowing was noted and suggested diffuse encephalopathy. *Id*. The conclusion was nine days of abnormal EEG monitoring due to frequent bifrontal independent epileptiform discharges indicating increased epileptogenic potential over the frontal region, greater on the right side than the left. *Id*. G.L.'s discharge diagnosis was localization related epilepsy. *Id*.

During 2015, G.L.'s diagnosis was changed to Dravet-type intractable epilepsy without identifiable genetic abnormality. Pet. Ex. 14 at 156-57. Her MRIs and genetic testing were normal and Dravet syndrome was ruled out. *Id*.; Pet. Ex. 31 at 1.

As of September 2017, G.L.'s diagnosis was "[i]ntractable epilepsy undetermined as to focal or generalized." Pet. Ex. 33 at 2. She was admitted to CCMC for continuous EEG monitoring on September 21, 2017. *Id*. at 15. Her last convulsive seizure occurred in May of 2017 and was associated with febrile illness; however, petitioner reported that G.L. had had six staring episodes in the past week. *Id*. G.L.'s EEG results were abnormal and consistent with generalized epilepsy. *Id*. at 48.

No further medical records have been filed.

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[17] A PET scan is a diagnostic test which uses radioactive chemicals to measure the metabolic activity of cells. In neurology, epilepsy can be identified as a localized area of increased metabolic activity indicating rapid nerve firing. *See Mosby's* at 763-65.

[18] Lamictal is the brand name for lamotrigine, an anticonvulsant used in the treatment of partial seizures. *Lamictal*, DORLAND'S at 1000; *lamotrigine*, *id*. at 1003.

C. Expert Reports

1. Petitioner's Expert, Dr. David Siegler[19]

Dr. Siegler opined that the varicella and pneumococcal vaccinations that G.L. received on April 16, 2012 caused her to develop a fever, which triggered her complex febrile seizures and later her development of intractable epilepsy. Pet. Ex. 15 at 3.

According to Dr. Siegler, fever is a common side effect of varicella and pneumococcal conjugate vaccinations; the package inserts for both vaccines list fever as an "expected complication." Pet. Ex. 15 at 2; *see also* Pet. Ex. 21 at 1,[20] Pet. Ex. 22 at 1, 9.[21] He added that febrile seizures are also "considered a risk" for the pneumococcal conjugate vaccine, but not the varicella vaccine. *Id*.

Dr. Siegler conceded that it is difficult to differentiate between "benign" febrile seizures and emerging epilepsy provoked by fever, since both can be provoked by fever. Pet. Ex. 15 at 2. However, 93 to 97% of children who experience febrile seizures do not develop epilepsy. *Id*., citing Pet. Ex. 17,[22] Pet. Ex. 18,[23] Pet. Ex. 19,[24] Pet. Ex. 20.[25] Of the small percentage of children who do develop epilepsy, there are two high risk groups, children with complex febrile seizures and children with neurologic abnormalities. Pet. Ex. 15 at 2. Complex febrile seizures are characterized by three features: a duration greater than 15 minutes, more than one seizure within 24 hours, and focal semiology.[26] *Id*. In Dr. Siegler's opinion, a child who has a complex febrile seizure with all three features of complexity is highly likely to develop epilepsy. *Id*.

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[19] Dr. Siegler received his medical degree from University of Texas Southwestern Medical School and completed residencies in pediatrics and child neurology at Stanford University. Pet. Ex. 16 at 3-4. He is board certified in neurology. *Id*. at 2. Dr. Siegler has appointments in the Department of Pediatrics at both Oklahoma University State College of Osteopathic Medicine and the University of Oklahoma College of Medicine. *Id*. at 1. He is "on staff" at Saint Francis Hospital and Saint John Hospital. Tr. 24. Dr. Siegler estimated that 95% of his time is spent actively practicing medicine. Tr. 21. He was qualified as an expert in pediatric neurology without objection. Tr. 19-25.

[20] Varivax package insert, Merck & Co. (2013), filed as "Pet. Ex. 21."

[21] Prevnar 13 package insert, Pfizer (2016), filed as "Pet. Ex. 22."

[22] John F. Annegers et al., *Factors Prognostic of Unprovoked Seizures After Febrile Convulsions*, 316 N. ENGL. J. MED. 493-98 (1987), filed as "Pet. Ex. 17" and "Resp. Ex. A, Tab 8."

[23] Mogens Vestergaard et al., *The Long-Term Risk of Epilepsy After Febrile Seizures in Susceptible Subgroups,* 165 AM. J. EPIDEMIOL. 911-18 (2007), filed as "Pet. Ex. 18."

[24] Karin B. Nelson & Jonas H. Ellenberg, *Predictors of Epilepsy in Children Who Have Experienced Febrile Seizures,* 295 N. ENGL. J. MED. 1029-33 (1976), filed as "Pet. Ex. 19."

[25] John F. Annegers et al., *The Risk of Epilepsy Following Febrile Convulsions*, 29 NEUROL. 297-303 (1979), filed as "Pet. Ex. 20."

[26] "Semiology" is another work for symptomatology. *Semiology*, DORLAND'S at 1690.

To support his opinion, Dr. Siegler referred to Pet. Ex. 17, a study which followed 687 children for an average of 18 years who had previously experienced an initial febrile seizure. Pet. Ex. 17 at 1-2. The authors looked at whether any of the subjects had subsequent unprovoked seizures, and if so, how many complex features were associated with the subsequent seizure. *Id*. Neurologically normal children who experienced complex febrile seizures with all three features had about a 50% likelihood of developing epilepsy. *Id*. at 5; Pet. Ex. 15 at 3. The study concluded that the chance that a child who had an initial febrile seizure would develop epilepsy increased with the number of complex features exhibited by that child in subsequent unprovoked seizures. *Id*. at 1.

Dr. Siegler also submitted Pet. Ex. 20, a study which "compared children with pre-morbid neurological abnormalities and neurologically normal children" with the type of febrile seizure each had, simple or complex. Pet. Ex. 15 at 2. For neurologically abnormal children, the risk of developing epilepsy was unaffected by whether the febrile seizure was simple or complex. *Id*. However, neurologically normal children were much more likely to develop epilepsy if they had a complex febrile seizure rather than a simple febrile seizure. *Id*. Based on these findings, the authors surmised that the neurologically abnormal children have a pre-existing propensity to have seizures without fevers. *Id.*

G.L. developed a fever the day after her varicella and pneumococcal vaccines but did not have any signs of illness; in Dr. Siegler's opinion, this indicates that G.L.'s fever was vaccine-induced. Pet. Ex. 15 at 2.

Dr. Siegler agreed with G.L.'s treating physicians that the initial and two subsequent seizures were correctly classified as complex febrile seizures; her initial seizure had all three features of complexity, a duration greater than 15 minutes, more than one seizure within 24 hours, and focal semiology. Pet. Ex. 15 at 1-2. Her second seizure event included two out of three complex features; her third seizure event only displayed one feature, but Dr. Siegler explained that this was because she was administered seizure medication shortly after the seizure began. *Id*. at 2. He noted that the third seizure occurred six days after G.L. received an MMR vaccination. *Id*.

According to Dr. Siegler, because G.L. had all three features of complex febrile seizures, she was at the "highest possible risk for developing epilepsy for a neurologically normal child." Pet. Ex. 15 at 2. One study found that children who exhibited all three complex features were more likely to develop subsequent unprovoked partial seizures.[27] *Id*.; Pet. Ex. 17 at 1. G.L. developed recurrent unprovoked seizures and was later diagnosed with intractable epilepsy. *Id*. at 1. Her clinical seizures and EEG suggest probable right frontal lobe epileptogenic focus with risk for secondary generalization although she has bilateral epileptiform discharges. *Id*.

Dr. Siegler opined that G.L.'s two complex febrile seizure events following her varicella-pneumococcal and MMR vaccinations, respectively, suggest that G.L. was predisposed to developing a fever following vaccination and to febrile seizures generally. Pet. Ex. 15 at 3. Doctors do not know why complex febrile seizures confer a greater risk of epilepsy, but "[t]here may be a genetic-environmental interaction in children like [G.L.] who may be genetically susceptible to having fever from vaccines and also susceptible to having seizures from fever." *Id.*

[27] An "unprovoked" seizure is one that is not triggered by fever, medication, etc.

Dr. Siegler concluded that G.L.'s first febrile seizure, with all three complex features, occurred without illness and within one day of varicella and pneumococcal vaccines. This strongly points to the vaccines as the cause of the fever that triggered her initial complex febrile seizure and later resulted in her development of intractable epilepsy. Pet. Ex. 15 at 3.

2. Respondent's Expert, Dr. Gregory Holmes[28]

Dr. Holmes agreed that the pneumococcal vaccine has been associated with febrile seizures but noted that the risk was very low; only 0.1% of children receiving their first dose had a febrile seizure. Resp. Ex. A at 12; Resp. Ex. A, Tab 4.[29] He further agreed with Dr. Siegler that there was little likelihood that a varicella vaccine would cause a febrile seizure. *Id*.; Resp. Ex. A, Tab 7.[30] However, according to Dr. Holmes, even if the pneumococcal vaccine caused a febrile seizure, it could not cause or trigger a seizure disorder. *Id*. at 13.

Dr. Holmes opined that, although complex febrile seizures have a higher association with epilepsy than simple febrile seizures, that does not mean that complex febrile seizures cause medically intractable epilepsy. Resp. Ex. A at 13, Resp. Ex. A, Tab 14.[31] Children with a history of febrile seizures develop a variety of types of epilepsy and are "not very different" from epilepsy in children who did not have febrile seizures. *Id*.; Resp. Ex. A, Tab 9;[32] Resp. Ex. A, Tab 10.[33] Similarly, the rate of occurrence of complex partial seizures in children who have had febrile seizures is almost the same as the rate in children who never had febrile seizures. *Id*.; Resp. Ex. A,

[28] Dr. Holmes received his medical degree from the University of Virginia and completed residencies in pediatric and pediatric neurology at Yale University School of Medicine and University of Virginia School of Medicine, respectively. Resp. Ex. B at 1. He is board certified in neurology and clinical neurophysiology. Tr. 70. He currently holds appointments in both pediatrics and neurological sciences at the University of Vermont College of Medicine. Resp. Ex. B at 2. Dr. Holmes also serves as the Physician Leader for the Neurology Health Care Service at Fletcher Allen Health Care. *Id*. About 40% of his time is spent on clinical work. Tr. 71. Dr. Holmes discussed his medical background and academic focus, including his interest in epilepsy and the cognitive effects of recurrent seizures on the developing brain. Tr. 71. He has written 398 peer reviewed articles, 120 review articles, and 75 chapters or books. Tr. 72. Dr. Holmes was offered and admitted as an expert in pediatric neurology. Tr. 72.

[29] Hung Fu Tseng et al., *Post-licensure Surveillance for Pre-specified Adverse Events Following the 13-valent Pneumococcal Conjugate Vaccine in Children*, 31 VACCINE 2578-83 (2013), filed as "Resp. Ex. A, Tab 4."

[30] Kathleen Stratton et al., eds., ADVERSE EFFECTS OF VACCINES: EVIDENCE AND CAUSALITY (2012), filed as "Resp. Ex. A, Tab 7."

[31] Miquel Raspall-Chaure, *The Epidemiology of Convulsive Status Epilepticus in Children: A Critical Review*, 48 EPILEPSIA 1652-63 (2007), filed as "Resp. Ex. A, Tab 14."

[32] Shlomo Shinnar, *Febrile Seizure and Mesial Temporal Sclerosis*, 3 EPILEPSY CURR. 115-18 (2003), filed as "Resp. Ex. A, Tab 9."

[33] Anne T. Berg et al., *Childhood-onset Epilepsy With and Without Preceding Febrile Seizures*, 53 NEUROL. 1742 (1999), filed as "Resp. Ex. A, Tab 10."

Tab 15.[34] This supports the hypothesis that febrile seizures do not contribute appreciably to the occurrence of complex partial seizures. *Id.*; Resp. Ex. A, Tab 15 at 3.

According to Dr. Holmes, "Complex febrile seizures appear to be an age-specific expression of seizure susceptibility in patients with an underlying seizure diathesis." *Id.* at 13; Resp. Ex. A, Tab 9. He added, "The tendency to have complex febrile convulsions likely reflects pre-existing brain disease that is also responsible for the subsequent development of partial epilepsy." *Id.*; Resp. Ex. A, Tab 8; Resp. Ex. A, Tab 16.[35] In other words, a child who has a complex febrile seizure most likely has an underlying brain abnormality which causes them to later develop epilepsy; the febrile seizure and the epilepsy are both manifestations of the same brain problem.

Like Dr. Siegler, Dr. Holmes relied on the 1987 Annegers study. *See* Pet. Ex. 17; Resp. Ex. A, Tab 8. Annegers suggested an association between complex febrile convulsions[36] and partial seizures, and "may reflect either a causal association or the presence of preexisting brain disease that is responsible for both the complex febrile seizures and later partial seizures." Resp. Ex. A at 12; Pet. Ex. 17. However, Dr. Holmes noted that the authors did not find a direct causal sequence between complex febrile seizures and temporal lobe epilepsy. *Id.* Rather, the authors concluded that "complex febrile seizures are not causally related to partial unprovoked seizures but rather indicate a preexisting brain abnormality underlying both." Pet. Ex. 17 at 6; Resp. Ex. A at 12-13.

Dr. Holmes agreed with Dr. Siegler that G.L.'s first seizure occurred following her varicella and pneumococcal vaccinations and that it was possible that the pneumococcal vaccine caused G.L.'s fever and febrile seizure. Resp. Ex. A at 12. Conversely, Dr. Holmes also suggested that G.L.'s seizure was caused by an infection, noting that she had an elevated white blood cell count upon admission to the hospital following her first seizure. *Id.* "While stressors such as seizures can result in peripheral leukocytosis, it is unlikely that a white count of this magnitude was caused by a seizure."[37] *Id.*; Resp. Ex. A, Tab 5;[38] Resp. Ex. A, Tab 6.[39] He further noted that

[34] C.M. Verity & Jean Golding, *Risk of Epilepsy After Febrile Convulsions: A National Cohort Study*, 303 BMJ 1373-76 (1991), filed as "Resp. Ex. A, Tab 15."

[35] Walter A. Rocca et al., *Risk Factors for Complex Partial Seizures: A Population-Based Case-Control Study,* 21 ANN. NEUROL. 22-31 (1987), filed as "Resp. Ex. A, Tab 16."

[36] Dr. Holmes uses "seizure" and "convulsion" interchangeably.

[37] Notably, G.L.'s treating doctors attributed G.L.'s elevated white blood cell count to her seizure activity and ruled out any infection. *See* Pet. Ex. 5 at 123, 141. Furthermore, her white blood cell count was normal the following morning without the administration of antibiotics.

[38] Metin Aydogan et al., *Transient Peripheral Leukocytosis in Children with Afebrile Seizures,* 22 J. CHILD NEUROL. 77-79 (2007), filed "Resp. Ex. A, Tab 5."

[39] Mohammad R. Mohebbi et al., *Peripheral Leukocytosis in Children with Febrile Seizures,* 19 J. CHILD NEUROL. 47 (2004), filed as "Resp. Ex. A, Tab 6."

subsequent immunization with pneumococcal vaccine did not result in fever.[40] *Id*.

According to Dr. Holmes, the "critical question in this case is whether the Prevnar13 (sic) pneumococcal vaccine resulted in the development of epilepsy in [G.L.]" Resp. Ex. A at 12. Dr. Holmes agreed that the initial complex febrile seizure preceded G.L.'s intractable epilepsy but maintained that the two were not connected. *Id*.

Dr. Holmes clarified that while fever can provoke seizures, that does not mean that febrile seizures cause epilepsy, "only that there is a predisposing tendency toward epilepsy which is provoked by the fever." Resp. Ex. A at 12. He noted that some children with an underlying predisposition to epilepsy will have their seizure associated with fever because fever lowers the seizure threshold. *Id*. at 11-12. This is a strong precipitating factor for seizures in children with epilepsy. *Id*.; Resp. Ex. A, Tab 2;[41] Resp. Ex. A, Tab 3.[42] Like G.L., "children with an underlying biological substrate for epilepsy will go on to develop seizures without fever." *Id*. at 12.

Dr. Holmes opined that G.L. has "medically intractable epilepsy of the focal secondarily generalized type" and noted that "[m]any children with focal epilepsy go on to develop medically intractable epilepsy." Resp. Ex. A at 11, citing Resp. Ex. A, Tab 1.[43] Based on the focal semiology of G.L.'s first seizure, she had a propensity to develop epilepsy. *Id*. at 13. In Dr. Holmes' opinion, there is no scientific evidence to support that G.L.'s complex febrile seizure resulted in an enduring medically intractable epilepsy. *Id*.

To support this point, Dr. Holmes pointed to data showing that a small number of children who have prolonged seizures develop acute hippocampal edema which evolves to mesial temporal sclerosis.[44] Resp. Ex. A at 13; Resp. Ex. A, Tab 11;[45] Resp. Ex. A, Tab 12;[46] Resp. Ex. A, Tab

[40] This statement by Dr. Holmes is inaccurate; G.L. received pneumococcal vaccinations on June 13, 2011, August 15, 2011, October 12, 2011, and April 16, 2012. *See* Pet. Ex. 2 at 1; Pet. Ex. 3 at 4. G.L. did not receive any additional pneumococcal vaccinations after the April 16, 2012 vaccinations.

[41] E. Balamurugan et al., *Perceived Trigger Factors of Seizures in Persons with Epilepsy*, 22 SEIZURE 743-47 (2013), filed as "Resp. Ex. A, Tab 2."

[42] Roland A. Bender et al., *Febrile Seizures and Mechanisms of Epileptogenesis: Insights from an Animal Model*, 548 ADV. EXP. MED. BIOL. 213-25 (2004), filed as "Resp. Ex. A, Tab 3."

[43] Mohammed M.S. Jan et al., *Convulsive Status Epilepticus in Children with Intractable Epilepsy is Frequently Focal in Origin*, 29 CAN. J. NEUROL. SCI. 65-67 (2002), filed as "Resp. Ex. A, Tab 1."

[44] *See supra*, n.11.

[45] Rod Scott et al., *Febrile seizures and mesial temporal sclerosis: No association in a long-term follow-up study*, 61 NEUROL. 588-89 (2003), filed as "Resp. Ex. A, Tab 11."

[46] Darrell V. Lewis et al., *Hippocampal Sclerosis After Febrile Status Epilepticus: The FEBSTAT Study*, 75 ANN. NEUROL. 178-85 (2014), filed as "Resp. Ex. A, Tab 12."

13.[47] However, there is no evidence on neuroimaging that G.L. developed edema or sclerosis as a result of her febrile seizures. *Id*. Further, in Dr. Holmes' opinion, febrile seizures can only cause temporal epilepsy, which G.L. does not have. *Id*. Dr. Holmes opined that there is no evidence that G.L.'s complex febrile seizures caused her to develop an epileptic focus in the frontal lobe. *Id*.

Dr. Holmes concluded that the pneumococcal vaccine was neither a cause nor a trigger for G.L.'s underlying seizure disorder. Resp. Ex. A at 13. G.L.'s first seizure was associated with a fever that lowered her seizure threshold to the point where she had a complex febrile seizure, with seizure semiology indicating right frontal lobe dysfunction. *Id*. at 13-14. She now has "medically intractable epilepsy with right front[al] area of onset." *Id*. at 13. In Dr. Holmes' opinion, G.L.'s clinical course was not influenced by any immunizations she received. *Id*. at 14.

D. Testimony and Affirmation

1. Petitioner, Kristen Silverio

Petitioner submitted that G.L. was a healthy baby girl, born full term via normal delivery without complications. Pet. Ex. 1 at 1. She received a "clean bill of health" at all of her well child checkups until her first adverse reaction. *Id*.; Tr. 11.

According to petitioner, on April 16, 2012, G.L. received pneumococcal and varicella vaccinations at her one-year-old well baby visit. Pet. Ex. 1 at 1; Tr. 11. The next morning, petitioner awoke to find G.L. seizing in her crib. *Id*.; Tr. 11. G.L.'s body was jerking uncontrollably, and she was "super hot." *Id*.; Tr. 11-12. G.L.'s father called 911. *Id*.; Tr. 12.

The paramedics arrived and administered Ativan, and the seizure subsided. Pet. Ex. 1 at 1-2; Tr. 12. Petitioner estimated that it was about 25 minutes from when she first found G.L. seizing to when the seizure subsided. *Id*. at 2; Tr. 12. Upon arrival at the ER at CCMC, G.L. began seizing again, this time affecting only her left side. *Id*.; Tr. 12-13. G.L. was diagnosed with "complex febrile seizure," "tonic-clonic lasting greater than 15 minutes." *Id*. She was admitted to the hospital with a fever of over 101 degrees and stayed for 48 hours for observation and testing. *Id*.; Tr. 12-13.

Petitioner recalled that the emergency room staff advised her that children can develop febrile seizures after a triggering event, such as a high fever, and once they have one, are prone to subsequent seizures every time they have a high fever. Pet. Ex. 1 at 2.

Petitioner affirmed that G.L. had another seizure on May 3, 2013. She described G.L. as "not acting like her usual self." Pet. Ex. 1 at 2. G.L. "did not have high fever, but she was warmer than usual." *Id*. G.L had another left-sided seizure which lasted about six minutes and stopped before Diastat was administered. *Id*. G.L. was taken to CCMC and examined by Dr. Culbertson who provided a primary diagnosis of "febrile seizure." *Id*. G.L. was released shortly thereafter. *Id*.

[47] Syndi Seinfeld, Howard P. Goodkin, and Shlomo Shinnar, *Status Epilepticus*, 6 COLD SPRING HARB. PERSPECT. MED. 1-13 (2016), filed as "Resp. Ex. A, Tab 13."

Petitioner recalled that later that day "around 7:30 p.m., G.L. started acting really funny again. She was repeating the same words over and over, and her hand was shaking uncontrollably." Pet. Ex. 1 at 2. G.L.'s eyes rolled to the side and "we realized she was having another seizure." *Id*.; Tr. 14. They called 911. *Id*.; Tr. 14. Initially, the paramedics said that G.L. was postictal from her seizure earlier that day, but after a discussion with petitioner, they placed an IV and transported G.L. back to CCMC, where she continued to seize. *Id*.; Tr. 14-15. Petitioner recalled that G.L.'s seizure lasted anywhere from 45 minutes to over an hour; they could not get her to stop seizing. Tr. 15. Petitioner affirmed that G.L. was "pumped…so full of medication that she stopped breathing. They were getting ready to intubate her when she finally started breathing on her own again…" Pet. Ex. 1 at 3. G.L. was kept in the PICU overnight. *Id*.; Tr. 15. The diagnosis was "abnormal febrile seizures" due to the length of the seizures. *Id*.

Petitioner affirmed that at 15 months of age, G.L. received the MMR vaccine and developed a fever six days later. Tr. 15-16. She was ultimately diagnosed with intractable epilepsy. Tr. 16. They were told that G.L. had partial-complex seizures and will continue to experience them. Pet. Ex. 1 at 3. The neurologist did genetic testing because they "wanted to know why all of a sudden [G.L. was having seizures] when she was fine." Tr. 16. The testing did not find any genetic mutations or underlying brain abnormalities, and there is no family history of epilepsy. Tr. 16, 18.

Petitioner stated that G.L. was taken to numerous medical providers to assess, diagnose and manage her seizures. She has had EEGs, MRIs, CAT scans, and x-rays, and exhausted many different seizure medications. Pet. Ex. 1 at 3. G.L. was examined in New York and determined not to be a good candidate for brain surgery. *Id*. At the time of the hearing, G.L. was on her ninth seizure medication. Tr. 16-17. The seizures have not gone away but occur less frequently, about five months in between events. Tr. 17. In addition to seizures, G.L. has horrible mood swings, with fluctuations in her appetite and weight and sensory issues. Pet. Ex. 1 at 3.

2. Dr. Siegler's Testimony

At hearing, Dr. Siegler explained that a febrile seizure is a seizure provoked by fever. Tr. 25. A "simple" febrile seizure is "a brief convulsion induced by a fever." Tr. 26. Simple febrile seizures are "relatively common" in children, and it is "very uncommon" for a simple febrile seizure to go on to become epilepsy. Tr. 27.

In contrast, "complex" febrile seizures are more than "just a convulsion." They can last longer than 15 minutes, they can be "focal," meaning they only affect one side of the body, and they can include multiple seizures within a 24-hour period. Tr. 27. Children with complex febrile seizures are more likely to develop epilepsy than children with simple febrile seizures. Tr. 28, 29. Because complex febrile seizures can be prolonged, the child can suffer from inadequate oxygenation and brain dysfunction; if the seizure cannot be stopped, the child is at risk for febrile status epilepticus. Tr. 28. These possibilities increase the likelihood of harm to the child. Tr. 28.

Dr. Siegler explained that the more features of complexity to the seizure, the greater the risk of epilepsy. Tr. 30. He cited data from a graph from Pet. Ex. 19 to illustrate his point.

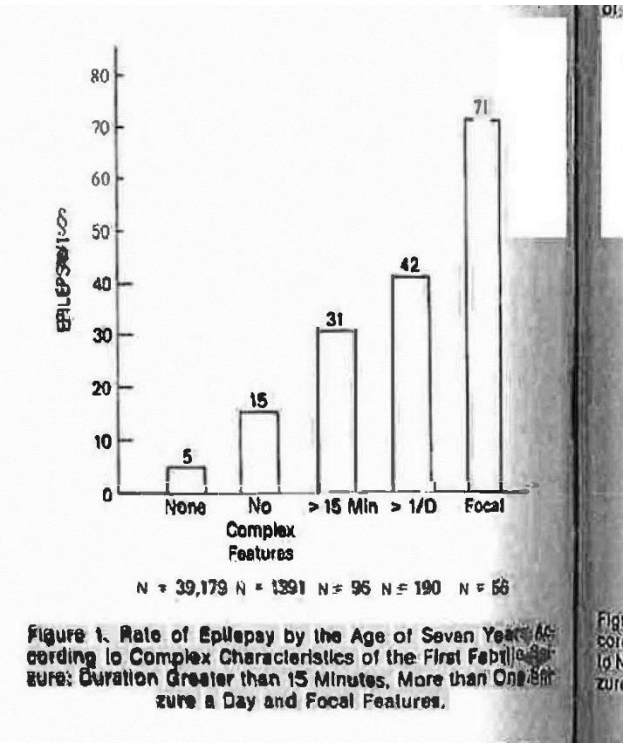

Figure 1. Rate of Epilepsy by the Age of Seven Years According to Complex Characteristics of the First Febrile Seizure: Duration Greater than 15 Minutes, More than One Seizure a Day and Focal Features.

A child who has never had a febrile seizure has a 0.5% chance of epilepsy, while a child who has had simple febrile seizures has a 1.5% chance of epilepsy. Tr. 30-31; Pet. Ex. 19 at 2. A child who has had a prolonged febrile seizure, a form of complex febrile seizure, has a 3.1% chance of epilepsy; a child who has had more than one febrile seizure within a day has a 4.2% chance. Tr. 31; Pet. Ex. 19 at 2. The highest risk group is "children with focal aspects to their complex febrile seizures," who have a 7.1% chance of epilepsy. Tr. 31; Pet. Ex. 19 at 2. The focal nature of the seizure alone increases the risk. Tr. 30-32, 71. Dr. Siegler also referred to data from Pet. Ex. 17, which indicated a 2.4% risk of epilepsy with baseline, or simple, febrile seizures. Tr. 33; Pet. Ex. 17 at 3. A complex seizure lasting longer than 10 minutes but less than 30 minutes that has focal features and repeated episodes raised the risk of epilepsy to 29%. Tr. 33-34. Dr. Siegler explained that a febrile seizure lasting longer than 30 minutes is considered "febrile status epilepticus." Tr. 35.

Dr. Siegler testified that G.L.'s first seizure was longer than 25 minutes, and perhaps longer than 30 minutes, by the time petitioner found her. Tr. 35-36. Dr. Siegler described both G.L.'s first and second febrile seizures as febrile status epilepticus. Tr. 35-36, 54. Dr. Siegler's testimony as to the length of these seizures differed from what was contained in his report and was apparently based on petitioner's testimony. In his report, Dr. Siegler repetitively referred to the initial seizures as being complex febrile seizures, lasting longer than 15 minutes with more than one event within 24 hours and focal semiology, but at hearing he referred to these seizures as "febrile status epilepticus" for the first time. Pet. Ex. 15 at 1-2; Tr. 35-36, 54. To that end, Dr. Siegler testified that one complex seizure lasting for 30 minutes or longer that is focal and repeated increases the statistical risk of epilepsy from 1.4 to 49%; in other words, it makes the child 35 times more likely to develop epilepsy. Tr. 36-38; Pet. Ex. 17 at 5. Having another complex febrile

event or cumulative events, like G.L., would place a child in the high-risk group for developing epilepsy. Tr. 38-40; Pet Ex. 20 at 4, Table 6.

Dr. Siegler submitted that neurologically normal children who experience febrile seizures with three features of complexity have about a 50% likelihood of developing epilepsy. Tr. 40-41; Pet. Ex. 15 at 3. Some normal children develop epilepsy and "you don't ever figure out" why. Tr. 60. In theory, however, these children have an inherent propensity or susceptibility to develop epilepsy. Tr. 42. It may be genetic, but not identified as a genetic abnormality. Tr. 42. Dr. Siegler suggested that an inflammatory event, or the seizure itself, which represents abnormal neuronal hyperexcitability, causes injury in these children. Tr. 42. "There's evidence that the genes can be affected and promote hyperexcitability. It could be neuronal networks. So something gets changed…and that susceptibility [to seizures] is enhanced." Tr. 42.

Dr. Siegler agreed that there are "probably a lot of genetic abnormalities that we haven't discovered yet…" but pointed out that G.L. did not have a family history of seizures, her genetic testing did not show any abnormalities, and her MRI findings did not show any brain abnormalities. Tr. 42, 61-62. In Dr. Siegler's opinion, there is no evidence that G.L. had a preexisting brain disease. Tr. 67-68. He emphasized that kids "like G.L. who are normal beforehand and develop febrile seizures, there's something about them that's different…it's not that they have a brain disease beforehand, but they developed some process that promoted the seizure, [and] the development of epilepsy." Tr. 63; Pet. Ex. 15 at 3. Dr. Siegler compared this susceptibility for epilepsy with the higher risk for skin cancer in fair-skinned red heads. Tr. 68. "I kind of liken it to a very pale redheaded person. They're not genetically abnormal…[but] they have the propensity for developing skin cancer." Tr. 68.

Dr. Siegler agreed that Annegers suggests that complex febrile seizures are causally related to temporal lobe epilepsy but points out that, though there is some support for cell death associated with prolonged seizures, the seizures must be considerably longer than usual, with prolonged febrile convulsions in humans for a direct causal relationship, which has not yet been determined. Tr. 63-64; Pet. Ex. 17 at 5-6. He further agreed that the authors proposed that the association between complex febrile convulsions and the subsequent development of partial epilepsy may reflect either a causal relationship between the two disorders or a preexisting brain disease that is responsible for both of them. Tr. 63-64, 67; Pet. Ex. 17 at 1.

Dr. Siegler conceded that one cannot parse out which of the complex febrile seizures G.L. suffered was responsible for her development of epilepsy but submitted that the first two seizures were the most likely to be responsible due to the prolonged nature of both seizures. Tr. 65-66. He suggested that the first seizure lowered G.L.'s seizure threshold and each subsequent seizure increased her risk of developing epilepsy. Tr. 66.

Dr. Siegler pointed to the Vestergaard study, which discusses three groups of children, those with a genetic abnormality, those with familial epilepsies or gene mutations, and those without any family history of epilepsy, like G.L. Tr. 44-45. According to Dr. Siegler, the Vestergaard study suggests that in these children, prolonged febrile seizures, a form of complex febrile seizure, causes changes in the brain. Tr. 45; Pet. Ex. 18 at 5. Vestergaard cited to the Chen article, which showed that "hyperthermia induced seizures may cause long-lasting modifications

of the brain, including channel, synapses, and neuronal networks within the hippocampus, which then leads to sustained dysfunction of the cells and a decreased seizure threshold." Tr. 45; *see generally* Pet. Ex. 29.[48] G.L. has no history of seizures and is "still normal," but has some process in her brain that does not affect her whole cognitive ability but is present and promoting recurrent focal seizures. Tr. 46. In Dr. Siegler's experience, it is common for MRIs to be normal despite recurrent febrile seizures, as they are in G.L.'s case. Tr. 47.

Dr. Siegler explained that on April 16, 2012, G.L. received vaccinations known to promote fever. Tr. 48. She developed a fever within 24 hours which induced a complex febrile seizure which was focal and prolonged. Tr. 48-49. She had a couple of seizures within a 24-hour period. Tr. 49. Her seizure was described in the record as right eye gaze with left-sided clonic activity associated with a fever of 102 degrees. Tr. 49-50; Pet. Ex. 5 at 107. Dr. Siegler read from the chart: "Although patient was febrile to 104, she has no focal source of infection with negative UA, urinalysis. Earlier exam, negative CSF cell counts. The fact that she received vaccines yesterday make it more likely that the fever is related to the vaccine, especially since…pneumovax and Varivax have both been associated with febrile seizures." Tr. 51; Pet. Ex. 5 at 123. The treating physicians considered the vaccines "more" likely the trigger of the seizures. Tr. 51.

Dr. Siegler addressed G.L.'s high CBC level in the emergency room following her first complex febrile seizures, attributing that to the stress reaction from the seizures. Tr. 51-52. Her treating doctors ran tests, but "nothing came back as abnormal" and "we know she wasn't infected, because they didn't do antibiotics." Tr. 52. G.L.'s doctors attributed her high CBC level to a stress reaction. Tr. 52-53. In Dr. Siegler's opinion the vaccinations induced G.L.'s fever, which triggered her febrile seizure. Tr. 53.

In sum, Dr. Siegler testified that G.L. was a normal healthy infant when she received vaccinations that caused a complex febrile seizure, which triggered neuronal hyperexcitability via either inflammatory or molecular pathways, and lowered her seizure threshold, increasing the risk of additional seizures and epilepsy. Tr. 58.

I asked Dr. Siegler why, specifically, it was the pneumococcal conjugate and varicella vaccines that instigated the fever and seizures as opposed to any of the vaccines that G.L. received in the first year of life, including her previous pneumococcal conjugate vaccinations, or any of the fevers she had from routine illnesses. Tr. 58-59. Dr. Siegler responded that he did not have an answer but noted that susceptibility to febrile seizures is highest from six months old to six years old. Tr. 59. He added that, if there were an explanation other than the vaccines G.L. received, we would not be at hearing. Tr. 59.

3. Dr. Holmes's Testimony

The experts agreed that pneumococcal and varicella vaccinations could cause a fever and a fever could provoke febrile seizures as seen in G.L. Tr. 100, 131-32. However, Dr. Holmes opined that fever cannot cause frontal lobe seizures, the kind that G.L. suffered, because febrile seizures cause injury (edema and inflammation) to the hippocampus, in the temporal lobe. Tr. 78-

[48] Kang Chen et al., *Febrile Seizures in the Developing Brain Result in Persistent Modification of Neuronal Excitability in Limbic Circuits*, 5 NAT. MED. 888-94 (1999), filed as "Pet. Ex. 29."

79. Dr. Holmes concluded the vaccines G.L. received had no involvement in her seizures and ultimate epilepsy. Tr. 72-73. He opined that G.L. had a brain abnormality in her frontal lobe which caused the complex febrile seizures and ultimately led to her development of intractable epilepsy. Tr. 81, 109.

During the hearing, Dr. Holmes agreed that there is "good evidence" that immunizations can result in a fever that triggers a febrile seizure but opined that there is no connection between complex febrile seizures and subsequent epilepsy of the frontal lobe. Tr. 100, 135. However, it is unlikely the pneumococcal vaccine that G.L. received on April 17, 2012 caused her complex febrile seizure the following day because epidemiological data indicates that the risk of seizure following the pneumococcal vaccine is low. Tr. 90. "It can cause fever, so it's possible that the fever led to the febrile seizure. But there may be—it's not—it's certainly—I think it's unlikely the cause." Tr. 90. He further agreed that the MMR vaccine can cause fever and febrile seizures within 6 to 14 days of administration. Tr. 131-32. G.L. had a febrile seizure 6 days after the MMR vaccine. Tr. 132-33.

Although Dr. Holmes agreed that the pneumococcal vaccine could cause a fever which resulted in a febrile seizure, he maintained that G.L.'s fever was due to infection. Tr. 90-93, 122. He noted that G.L.'s white count was elevated at 33,900; in his opinion, this is too high to be leukocytosis related to seizure and indicates infection. Tr. 91-93. Dr. Holmes submitted two articles on leukocytosis in support of this opinion. Tr. 93; *see generally* Resp. Ex. A, Tabs 5 and 6. Dr. Holmes agreed that G.L.'s physicians did not find any evidence of infection and did not treat G.L. for an infection but did not agree with their assessment that G.L.'s increased white blood cell count resulted from a stress reaction to her seizure. Tr. 123-24.

Dr. Holmes added that even if the vaccines caused G.L.'s initial seizure, studies show that the outcome is the same for children who get a vaccine and have a febrile seizure versus children who have had a febrile seizure that is not associated with a vaccine. Tr. 94. He stated that fever is trigger for epilepsy, and G.L. is evidence that fever will trigger a complex seizure in a child with underlying epilepsy before epilepsy is diagnosed in that child. Tr. 76-77. Dr. Holmes cited to an article by Balamurugan et al. to support this opinion, stating that the article "indicates that fever is a trigger for people – for seizures in people that have epilepsy." Tr. 77; Resp. Ex. A, Tab 2.[49] Dr. Holmes also referenced an article by Raspall-Chaure et al. for support, explaining that Raspall-Chaure conducted a critical review of the epidemiology of convulsive status epilepticus in children, and found that the underlying etiology of the febrile seizure, rather than the febrile seizure itself, determined whether the child would develop epilepsy or not. Tr. 78; Resp. Ex. A, Tab 14. He added, "…a brain that has an abnormality prior to the febrile seizure, it's much more likely to go into status [epilepticus] than one that's not." Tr. 99.

However, he did not agree with Dr. Siegler's theory that repeated febrile seizures following vaccination could cause or trigger epilepsy. Tr. 72-73, 80. Dr. Holmes explained that a febrile

[49] More specifically, however, this article studied a variety of triggering factors in people who were older than nine years of age and had an "unequivocal diagnosis of epilepsy" prior to their participation in the study. Resp. Ex. A, Tab 2 at 1.

seizure is a generalized seizure[50] rather than a focal seizure.[51] Tr. 82. For a person to have a febrile seizure with focality, there would have to be brain disease prior to the febrile seizure. Tr. 82. Dr. Holmes stated that G.L. "has a pathological lesion in the right frontal lobe of the brain that's causing her seizures." Tr. 73. He cited to Annegers, quoting, "The tendency to have complex febrile convulsions reflects preexisting brain disease that is also responsible for the subsequent development of partial epilepsy." Tr. 79-80; Resp. Ex. A, Tab 8 at 6.

Dr. Holmes further stated, "G.L. has localization-related epilepsy with or without secondary generalization, also called focal epilepsy… [of] the right frontal lobe, so she has right frontal lobe epilepsy..." Tr. 72. By definition, a person with epilepsy has a brain abnormality; a "normal" brain cannot develop epilepsy. Tr. 73-74. According to Dr. Holmes, frontal lobe epilepsy is caused by an abnormality, or lesion, in the frontal lobe, occipital lobe epilepsy is caused by a lesion in the occipital lobe, and temporal lobe epilepsy is caused by a lesion in the temporal lobe. Tr. 104. He repeatedly emphasized that, because G.L. has epilepsy, she has an abnormality of the brain. Tr. 74, 109, 111.

Although it was pointed out that G.L.'s genetic testing and MRIs were normal, Dr. Holmes maintained that G.L. could still have an underlying brain abnormality, stating lesions are not always apparent on MRI, CT, or EEG unless the test is performed while the person is having a seizure; it could also be a "functional" lesion, meaning there is a "functional problem with those neurons that are not functioning normally." Tr. 74, 105. "She's got epilepsy. Epilepsy is a disorder of neural conductivity. It's an episode of excitatory inhibitory imbalance. She's got epilepsy. Not all people have a defined structural abnormality on MRI." Tr. 112. When asked what G.L.'s underlying brain abnormality was, Dr. Holmes said, "I'd only be speculating, but…" and could not offer an explanation. Tr. 109.

Dr. Holmes agreed that there is an extremely high correlation between complex febrile seizures and epilepsy. Tr. 109. He further agreed with the data from Annegers, which found that the more features of complexity in a febrile seizure, the higher the risk of developing epilepsy; he added that the risk would increase even further if the child had "mental retardation" or cerebral palsy. Tr. 106-08; Pet. Ex. 17 at 3; Resp. Ex. A, Tab 8 at 3. Dr. Holmes agreed that complex febrile seizures, particularly those with all three complex features, are a clear indicator of subsequent development of epilepsy. Tr. 132-33. However, he stressed that "association does not equate to causation." Tr. 102-03. He read aloud from his expert report:

> The fact that complex febrile seizures have a higher association with epilepsy than simple febrile seizures does not mean that complex febrile seizures can cause medically intractable epilepsy. Although there's an association between the occurrence of local febrile convulsions and later complex partial seizures, the ratio between afebrile tonic-clonic seizures and complex partial seizures in children who have had febrile convulsions is almost the same as in children who never had a

[50] A generalized seizure begins with abnormal electrical discharges in both hemispheres and manifests as widespread epileptiform activity. *See Pediatric Neurology: Principals & Practice* 991 (Swaiman, Ashwal & Ferriero eds., 4th ed. 2006) [hereinafter "*Pediatric Neurology*"].

[51] Dr. Holmes agreed that "complex partial seizures are focal seizures." Tr. 102-03.

> febrile convulsion. These findings are compatible to hypotheses that febrile convulsions do not contribute appreciably to the occurrence of partial seizures.

Resp. Ex. A at 13.

Dr. Holmes added that other special masters have cited to a 1987 book chapter[52] he wrote about febrile seizures, which discussed the Nelson and Ellenberg study[53] and looked at risk factors for developing epilepsy after febrile seizures, noting that the special master(s) concluded that because there is a risk factor for having epilepsy after a complex febrile seizure, epilepsy is therefore caused by complex febrile seizures. Tr. 89; *see also Stone v. HHS*, No. 04-1041V, 2011 WL 836992 (Fed. Cl. Spec. Mstr. Jan. 20, 2011), *mot. for rev. denied*, 99 Fed. Cl. 187 (2011), *aff'd* 676 F.3d 1373 (Fed. Cir. 2012); *Simon v. HHS*, No. 05-941V, 2007 WL 1772062 (Fed. Cl. Spec. Mstr. June 1, 2007). Dr. Holmes stated that these findings were "totally erroneous," and "it would have been nice" if they had read the entire chapter, because it states "…there is no evidence that febrile seizures lead to the onset of afebrile seizures…." Tr. 88. He found the Court's findings "irritating." Tr. 88-89.

To support his assertion that febrile seizures do not cause epilepsy, Dr. Holmes offered Verity, a 1991 study which surveyed approximately 16,000 infants born in 1970. Tr. 86; *see generally* Resp. Ex. A, Tab 15. 398 children had at least one febrile seizure; of 382 "neurologically normal" children who had febrile seizures, 305 children had a simple febrile seizure and 77 had a complex febrile seizure. Tr. 87; Resp. Ex. A, Tab 15 at 1. 32 children had prolonged febrile seizures; three of those children developed afebrile complex partial seizures. Tr. 87; Resp. Ex. A, Tab 15 at 1. Verity noted that the risk of developing epilepsy was highest for children who had focal febrile seizures. Resp. Ex. A, Tab 15 at 1. Dr. Holmes stated that Verity concluded, if febrile seizures caused brain damage that leads to later epilepsy, it is a rare occurrence. Tr. 86-87. He further noted that Verity stated, "The tendency to have complex febrile convulsions may reflect pre-existing brain disease that is also responsible for the subsequent development of partial epilepsy…" Resp. Ex. A, Tab 15 at 3; Tr. 85. Dr. Holmes then offered the Rocca article, which concluded that "neurological and developmental status prior to febrile seizure, and characteristics of febrile seizures are important predictors of subsequent epilepsy." Tr. 84; Resp. Ex. A, Tab 16 at 8.

Following a long exchange with me, Tr. 112-21, Dr. Holmes agreed that vaccines can cause fever, and fever can cause seizures. Tr. 116-17. If edema had been found in the hippocampus in this case, he would agree that G.L.'s vaccinations were the cause. Tr. 117-22. However, G.L.'s seizures generate from the frontal lobe, and in Dr. Holmes's opinion, cannot be caused by vaccination. Tr. 121. According to Dr. Holmes, it is "highly, highly unlikely" that G.L.'s febrile seizure, despite its complex focal nature, led to her intractable epilepsy. Tr. 119.

Dr. Holmes explained that only temporal lobe epilepsy, not frontal lobe epilepsy, can be caused by febrile seizures. Tr. 78-79. He based this opinion on a review of medical literature in

[52] The book chapter was not filed into the record for the Court's consideration.

[53] This study was filed by petitioner as Pet. Ex. 19, *see supra* n.24, and later filed into the record by respondent as Resp. Ex. C, Tab 8.

which he only found articles discussing a relationship between complex febrile seizures and temporal lobe epilepsy. Tr. 135-36. He stated that he could not find any articles looking at complex febrile seizures and frontal lobe epilepsy. Tr. 135-36.

He stated that Berg found no evidence that prolonged or focal febrile seizures were associated with localization related epilepsy or temporal lobe epilepsy *per se*. Resp. Ex. A, Tab 10; Tr. 136, 141. However, he agreed that the study lumped together simple febrile seizures with complex febrile seizures, which skewed the data. Tr. 140-42. Conversely, he also offered the Vestergaard study, which "shows that a prolonged seizure *can* lead to temporal lobe epilepsy." Tr. 137 (emphasis added). According to Vestergaard, prolonged febrile seizures can cause acute swelling of the hippocampus, suggesting that hyperthermia-induced seizures may cause longstanding modifications to channel synapses in neuronal networks within the hippocampus, leading to sustained dysfunction of these cells and a decreased seizure threshold. Tr. 137. This means that a prolonged febrile seizure could injure the hippocampus, leading to an alteration in the seizure threshold and causing temporal lobe epilepsy to develop. Tr. 137; Pet. Ex. 18 at 5. Dr. Holmes also referenced a letter to the editor of the journal *Neurology* emphasizing that temporal lobe sclerosis, rather than frontal lobe sclerosis, could occur following febrile seizures. "…you can see that the majority –it's about [the] hippocampus." Tr. 138; Resp. Ex. A, Tab 11.

Dr. Holmes explained that hyperthermic seizures can lead to a hyperexcitable neuronal network, which is an imbalance between excitatory and inhibitory activity. Tr. 130-31. Too much or too little of either excitation or inhibition can lead to a seizure. Tr. 130. Neuronal excitability, generally, is not limited to the hippocampus or the temporal lobe; it can affect the right frontal lobe and did so in G.L.'s case. Tr. 124-25. When asked how status epilepticus could cause neuronal excitability resulting in temporal lobe epilepsy, Dr. Holmes stated:

> So if we're going to talk about status epilepticus, a prolonged seizure, a hyperthermic seizure, say 40, 45 minutes, this can lead to hippocampal injury. This can lead to morphological – structural changes in the hippocampus. And it can lead to a persistent state of hyperexcitability, which is why these rats or humans can go on to develop epilepsy. A complex partial seizure does not alter fundamentally the excitability of the brain.

Tr. 131; *see also* Tr. 125, Pet. Ex. 29.

According to Dr. Holmes, studies have not been able to replicate brain damage with seizures less than 45 minutes long. Tr. 126. "…so we've gone to 45 minutes as the – sort of the minimum point for a seizure to occur." Tr. 126. Dr. Holmes emphasized the study found that hyperthermic seizures lead to changes only in the hippocampus. Tr. 125-26. "So when you look at these animals after the prolonged febrile – the hyperthermic seizures, what they have are temporal lobe seizures." Tr. 126; Pet. Ex. 29. Dr. Holmes agreed that the rats used in the Chen and Baram study did not have preexisting brain abnormalities. Tr. 127-28; Pet. Ex. 29.

When asked if a 25-minute seizure was considered a brief seizure, Dr. Holmes responded that it was, adding that there is no evidence that a seizure less than 30 minutes and even between 30 to 60 minutes would cause harm. Tr. 97. Dr. Holmes added that the FEBSTAT study is

following children who had febrile seizures of 30 minutes and longer; after the seizure, some children have edema in the hippocampus on MRI scans. Tr. 98. Years later, though, some have mild cognitive defects but so far, none have developed epilepsy. Tr. 98. It appears that febrile seizures over 30 minutes long can lead to mesial temporal sclerosis, or scarring on the hippocampus; however, Dr. Holmes stressed, this is only in the temporal lobe. Tr. 98. There is no evidence in any study that prolonged febrile seizures, even status epilepticus, leads to right frontal lobe epilepsy, which is what G.L. has. Tr. 99.

Dr. Holmes conceded that until the hearing when he heard the petitioner's testimony, he did not appreciate that G.L.'s first seizure was longer than 25 minutes. Tr. 121. He had concentrated on complex partial seizures, defined as more than one seizure in 24 hours, prolonged over ten minutes, and focal. Tr. 121.

The key source of contention during the hearing was Dr. Holmes' ultimate conclusion that that febrile seizures, complex febrile seizures, or even convulsive status epilepticus cannot cause frontal lobe damage. He opined that, while children with status epilepticus lasting hours or days sustain widespread brain damage, children with shorter convulsive seizures only have damage to the hippocampus, in the temporal lobe. Tr. 102. According to Dr. Holmes, "It wouldn't be a right frontal lobe, it would make no sense in why that would occur. It's either very diffuse or if it's just part of the brain, it's going to be [the] hippocampus." Tr. 102.

What was clear at hearing was not whether the subject vaccines can cause fever, or whether the fever could cause seizures, or even if complex febrile seizures could cause epilepsy, but that the source of disagreement was whether complex febrile seizures can cause frontal lobe epilepsy. Dr. Holmes maintained at hearing that G.L.'s intractable epilepsy of the frontal lobe was caused by a lesion in the frontal lobe.[54] Tr. 116, 118, 120. I asked Dr. Holmes to succinctly state his position, to which he responded:

> Yeah, I don't know how much I can—I don't know what else I can say. I went through her history. She came in and she had a Todd's paralysis following her first seizure, indicating to me that there is—that she was predisposed to having this seizure and that she has pathology in the right frontal lobe. I then cited a lot of literature indicating that there's no evidence that a complex partial seizure will lead to intractable epilepsy. That was all in my report. I don't know what's missing here.

Tr. 120.

E. Evidence Submitted Post-Hearing

1. Dr. Siegler's Supplemental Report

Dr. Sielger was asked to provide a supplemental report to address Dr. Holmes' opinions that G.L.'s epilepsy was caused by a lesion in the frontal lobe, that fever cannot cause frontal lobe

[54] Dr. Holmes raised this point in his expert report, *see* Resp. Ex. A at 13, but did not fully develop it until hearing; therefore, petitioner was allowed the opportunity to file a supplemental report from Dr. Siegler following the hearing to address this issue.

seizures, and that it is biologically implausible for complex febrile seizures to result in frontal lobe epilepsy.

Dr. Siegler agreed that it is more common to develop temporal lobe epilepsy following repetitive complex febrile seizures, but literature shows that extratemporal and generalized epilepsy do occur as a result of complex febrile seizures; therefore, it is not impossible or biologically implausible for repetitive complex febrile seizures to result in epilepsies localized outside of the temporal lobe. Pet. Ex. 34 at 3. He offered several articles in support of this opinion. The Hamati-Haddad[55] study demonstrated that children with a history of febrile seizures developed epilepsy occurring in areas of the brain other than the temporal lobe at a higher rate than children without a history of febrile seizures. Pet. Ex. 34 at 3; Pet. Ex. 38 at 1. Szabo[56] studied ten patients with complex partial status epilepticus and found hemodynamic and tissue changes in the hippocampus, thalamus, and other cortical regions, indicating that complex partial status epilepticus can cause changes in the brain outside of the temporal lobe. Pet. 34 at 3; Pet. Ex. 39 at 1. Donaire[57] observed cortical necrosis in two patients following repeated seizures, suggesting that the damage was caused by increase in metabolic demand for glucose and oxygen with compensatory increased demand in cerebral blood flow; such a demand, if insufficient, causes neuronal energy failure accompanied by lactate accumulation, which leads to hypermetabolic neural necrosis. Pet. Ex. 34 at 3-4; Pet. Ex. 40 at 2. Katramados[58] evaluated 36 patients without a history of idiopathic or symptomatic generalized epilepsy who developed partial status epilepticus, concluding that though it was a small sample size, partial status epilepticus can cause extratemporal cortical injury in several areas of the brain, including the frontal lobe. Pet. Ex. 34 at 4; Pet. Ex. 41 at 9.

In response to Dr. Holmes's testimony that febrile status epilepticus in rats can result in hippocampal injury and epilepsy, Dr. Siegler submitted a review article authored by Dr. Holmes which recognized that early life seizures disrupt critical periods of development. Pet. Ex. 34 at 4; Pet. Ex. 42.[59] This can result in morphological and functional changes, including changes in excitatory and inhibitory neurotransmissions in the neocortex. Pet. Ex. 34 at 4; Pet. Ex. 42 at 1.

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[55] Aline Hamati-Haddad & Bassel Abou-Khalil, *Epilepsy Diagnosis and Localization in Patients with Antecedent Childhood Febrile Convulsions*, 50 NEUROL. 917-22 (1998), filed as "Pet. Ex. 38."

[56] Kristina Szabo et al., *Diffusion-Weighted and Perfusion MRI Demonstrates Parenchymal Changes in Complex Partial Status Epilepticus*, Brain 1-8 (2005) filed as "Pet. Ex. 39."

[57] A. Donaire et al., *Cortical Laminar Necrosis Related to Prolonged Focal Status Epilepticus*, 77 J. NEUROL. NEUROSURG. PSYCHIATRY 104-06 (2006), filed as "Pet. Ex. 40."

[58] Angelos M. Katramados et al., *Peri-ictal Diffusion Abnormalities of the Thalamus in Partial Status Epilepticus*, 50 EPILEPSIA 265-75 (2009), filed as "Pet. Ex. 41."

[59] Gregory L. Holmes, *Effect of Seizures on the Developing Brain and Cognition*, 23 SEMIN. PEDIATR. NEUROL. 120-26 (2016), filed as "Pet. Ex. 42."

Dr. Siegler further noted that Dr. Holmes co-authored a study which found that "recurrent seizures in infancy result in a persistent enhancement of neocortical excitability." Pet. Ex. 43[60] at 1; Pet. Ex. 34 at 4. Dr. Siegler offered these results as experimental evidence to support his theory that prolonged complex febrile seizures can result in functional changes in the excitation-inhibition balance within the subcortical network, resulting in an increased susceptibility to seizures. Pet. Ex. 34 at 5.

Dr. Siegler submitted that the testimony at hearing confirmed that G.L. developed a fever the day after her vaccinations, which occurs in many neurologically normal children. Pet. Ex. 34 at 2, 5. The fever lowered her seizure threshold, which contributed to her first cluster of complex febrile seizures. *Id*. He pointed out Dr. Holmes' agreement that G.L.'s vaccinations could cause fever and that vaccine-induced fever could provoke febrile seizures. *Id*. at 1. In Dr. Siegler's opinion, petitioner's description of G.L.'s seizure activity exceeding 30 minutes supports the conclusion that G.L. experienced febrile status epilepticus the day following her vaccination. *Id*. at 2. He referenced the literature discussed at hearing which shows that complex febrile seizures, particularly those showing three features of complexity like G.L.'s, have a significantly higher risk of developing into epilepsy than those with simple febrile seizures or children without febrile seizures. *Id*.; *see* Pet. Ex. 17; Pet. Ex. 19; Pet. Ex. 20. Dr. Siegler pointed out that Dr. Holmes agreed that complex febrile seizures with three features of complexity are "risk factors for the subsequent development of epilepsy." Tr. 133; Pet. Ex. 34 at 2.

In response to Dr. Holmes's position on G.L.'s elevated white blood cell count of 33,900 being an infection, Dr. Siegler pointed out that G.L.'s treating physicians attributed this elevation to her seizures. He offered literature stating that seizures can caused elevated white blood cell counts as high as 50,000. Pet. Ex. 34 at 1; *see also* Pet. Ex. 37.[61] Dr. Siegler added that the absence of infectious signs or symptoms and the onset of fever within 24 hours of G.L.'s vaccinations indicates that the fever was most likely caused by the vaccinations. *Id*.

Less than three weeks later, G.L. developed a febrile illness and suffered another febrile status epilepticus cluster, which included a nearly two-hour cluster of continuous seizures. Pet. Ex. 34 at 5. According to Dr. Siegler, G.L.'s complex febrile seizure cluster induced a neuronal network inhibitory-excitatory imbalance which increased her susceptibility to seizures. *Id*. "The initial cortical changes were likely augmented, although not visualized on the brain MRI nine days later (perhaps too late to see transitory DWI changes). G.L. then had several additional febrile seizures. Eventually the cortical changes manifested in epilepsy." *Id*. Dr. Siegler opined that literature supports that prolonged febrile seizures can induce functional brain changes in the cerebral cortex resulting in increased susceptibility for epilepsy. *Id*.

Dr. Siegler posited that the issue here is whether a functional lesion existed before G.L.'s first febrile seizure or developed as a result of the febrile seizures. Pet. Ex. 34 at 3. He noted that

[60] Elena Isaeva et al., *Recurrent Neonatal Seizures Result in Long-Term Increase of Neuronal Network Excitability in the Rat Neocortex*, 31 EUR. J. NEUROSCI. 1446-55 (2010), filed as "Pet. Ex. 43."

[61] Neil Abramson & Becky Melton, *Leukocytosis: Basic of Clinical Assessment*, 62 AM. FAM. PHYSICIAN 2053-60 (2000), filed as "Pet. Ex. 37."

G.L.'s birth and neurodevelopment prior to the onset of febrile seizures were normal, which argued against a symptomatic seizure focus in the right frontal lobe. *Id*. He conceded that structural brain lesions can present with seizures later in life. *Id*. He further conceded that the absence of a brain lesion on the May 18, 2012 MRI did not disprove a seizure-induced right frontal lobe cortical dysfunction, which could have placed G.L. at risk for developing epilepsy, consistent with Dr. Holmes' testimony of a "functional lesion." *Id*. Therefore, in Dr. Siegler's opinion, "If [a lesion] was present prior [to G.L.'s first seizure], it had not become symptomatic until G.L. developed a vaccine-induced fever which triggered her first febrile seizure cluster. There is evidence that a functional lesion can develop in the cortex from seizures." *Id*.

In sum, Dr. Siegler proffered that G.L.'s clinical history, the known risk of complex febrile seizures developing into epilepsy, and experimental and clinical evidence of the connection between seizure activity and cortical dysfunction is the basis for petitioner's position that G.L.'s pneumococcal and/or varicella vaccinations on April 16, 2012 caused a fever that triggered a complex febrile seizure within 24 hours of vaccination. Pet. Ex. 34 at 5. The seizure activity induced a cortical response in G.L.'s right frontal lobe that contributed to or was augmented by her next episode of status epilepticus induced by a febrile illness. *Id*. Fever is a probable provocative event in the induction of a right frontal cortical excitatory-inhibitory imbalance, or "functional lesion," as an epileptogenic focus for G.L.'s development of epilepsy. *Id*. As presented, both human and animal studies show seizure-induced changes occur in areas of the brain outside of the hippocampus, and as in G.L.'s case, in the cerebral cortex. *Id*. These changes have been shown to increase the brain's susceptibility to seizures. *Id*. The literature presented showed both transitory and permanent imaging changes and physiologic "functional" changes in neuronal network excitability, which supports the theory that G.L.'s frontal lobe epilepsy developed from vaccine-induced, fever-triggered complex febrile seizures. *Id*. at 5-6.

2. Dr. Holmes' Supplemental Report

Dr. Holmes noted that Dr. Siegler made "numerous erroneous statements" in his supplemental report, which Dr. Holmes attributed to his own inability to "clearly articulate [his] opinion" in this matter and not to any misrepresentations by Dr. Siegler. Resp. Ex. C at 1. Similarly, Dr. Holmes stated that the characterization of his testimony in my post-hearing Order that "it is 'biologically implausible' for complex febrile seizures to result in a focal seizure in the frontal lobe" is wrong. *Id*. According to Dr. Holmes, "The correct statement would be that I believe it is biologically implausible for a complex febrile seizure to result in chronic frontal lobe epilepsy in a child *without a predisposing seizure focus in the frontal lobe*." *Id*. (emphasis added). It was ultimately Dr. Holmes's opinion in this case that febrile status epilepticus can only lead to temporal lobe epilepsy. *Id*. at 6.

Dr. Holmes reiterated his opinion that complex febrile seizures cannot cause epilepsy, explaining that literature strongly supports that children with complex febrile seizures are at a higher risk for developing epilepsy than children with simple febrile seizures, but this does not demonstrate that complex febrile seizures cause subsequent epilepsy. Resp. Ex. C at 3. According to Dr. Holmes, there are many triggers for seizures, including fever; none of them cause epilepsy. *Id*. He noted that children with febrile seizures from vaccines are at no greater risk of developing epilepsy than children who have febrile seizures from other causes. *Id*. Furthermore, in Dr.

Holmes' opinion, children with an underlying biological predisposition for epilepsy will eventually develop seizures regardless of fever. *Id*. "Epidemiological and mechanistic data strongly indicate that the 'tendency to have complex febrile convulsions reflects preexisting brain disease that is also responsible for the subsequent development of partial epilepsy.'" *Id*.

Despite acknowledging that a febrile seizure lowers the seizure threshold and can predispose a child to developing epilepsy, Dr. Holmes disagreed with Dr. Siegler's suggestion that "seizures beget seizures." Resp. Ex. C at 3, 7. He pointed out that a large percentage of children with epilepsy outgrow it, and "few patients show a progressive increase in severity or duration of their seizures over time." *Id*. at 7. According to Dr. Holmes, "remission" from epilepsy "is likely to be secondary to the overall decrease in excitability of the brain that occurs with age as well as with age-specific effects of gene activation and deactivation." *Id*. There are "a number of factors that determine which children with early life seizures will or will not go on to develop chronic epilepsy." *Id*.

Dr. Holmes conceded that febrile status epilepticus has been associated with a higher risk of epilepsy in general and temporal lobe epilepsy in particular, "'but until recently it has been difficult to distinguish association from causal relationship.'" Resp. Ex. C at 6, quoting Resp. Ex. C, Tab 24[62] at 3. He referenced a prospective study of children with febrile status epilepticus, noting that memory problems arose specifically in children with acute hippocampal injury on post-febrile status epilepticus MRI. *Id*.; *see also* Resp. Ex. C, Tab 27[63] (FEBSTAT study article concluding that febrile status epilepticus can result in acute hippocampal injury); Resp. Ex. C, Tab 28[64] (Examining the cognitive and developmental effects of febrile status epilepticus). The preponderance of the data is now in favor of a causal relationship between febrile status epilepticus and temporal lobe epilepsy but not with other forms of epilepsy. *Id*. Thus, Dr. Holmes's opinion that febrile status epilepticus cannot cause frontal lobe epilepsy.

In response to the literature that Dr. Siegler submitted in support of a connection between febrile status epilepticus and frontal lobe epilepsy, Dr. Holmes stated that none of the literature submitted by Dr. Siegler applies to this case. Resp. Ex. C at 5. In Dr. Holmes's opinion, the articles are not relevant to this matter because the studies were not performed on infants and the subjects of the studies had MRI abnormalities, while G.L. was 12 months old when she had her first febrile seizure and had no abnormalities on MRI. *Id*. at 5-6.

He further opined that Dr. Siegler misinterpreted the Hamati-Haddad study, stating that the study concluded that "the association between extratemporal epilepsy and antecedent febrile convulsions are at best weak and it is unlikely that febrile convulsions have an etiologic role in

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[62] Katelin P. Patterson et al., *Origins of Temporal Lobe Epilepsy: Febrile Seizures and Febrile Status Epilepticus*, 11 NEUROTHERAPEUTICS 242-50 (2014), filed as "Resp. Ex. C, Tab 24."

[63] Darrell V. Lewis et al., *Hippocampal Sclerosis after Febrile Status Epilepticus: The FEBSTAT Study*, 75 ANN. NEUROL. 178-85 (2014), filed as "Resp. Ex. C, Tab 27."

[64] Erica F. Weiss et al., *Cognitive Functioning One Month and One Year Following Febrile Status Epilepticus*, 64 EPILEPSY BEHAV. 283-288 (2016), filed as "Resp. Ex. C, Tab 28."

extratemporal lobe epilepsy." Resp. Ex. C at 4. Dr. Holmes stated the number of patients with extratemporal epilepsy preceded by febrile seizures was not statistically significant and submitted that the authors noted that febrile seizures do not "appear to be a clear risk factor for extratemporal epilepsy." *Id*. (citing Pet. Ex. 38 at 1); *but see* Pet. Ex. 38 at 3 ("Although complex FC were more likely to be seen in TLE (80.85) than ETE (66.7%), the difference was not significant.").

In contrast, Dr. Holmes offered his own laboratory's studies done in conjunction with Dr. Baram which studied a rat model of childhood febrile status epilepticus where they induced hyperthermic seizures in infant rats. Resp. Ex. C at 7; *see generally* Resp. Ex. C, Tab 32[65] (Measuring the effects of febrile status epilepticus on brain metabolic responses in juvenile rats); Resp. Ex. C, Tab 33[66] (Examining the effects of febrile status epilepticus on hippocampal function in rats); Resp. Ex. C, Tab 35[67] (Identifying significant memory problems in male rats following experimental prolonged febrile status epilepticus). The rats went on to develop temporal lobe epilepsy with abnormal cells in the hippocampus but had no discernable evidence of frontal lobe damage and did not have seizures arising from the frontal lobe. *Id*.; *but see* Resp. Ex. C, Tab 34[68] at 2 (Finding that experimental febrile seizures resulted in cognitive dysfunction in the hippocampus and prefrontal cortex networks). According to Dr. Holmes, this model is comparable to G.L., though extrapolating rats to children is difficult and G.L. does not have temporal lobe epilepsy or evidence of temporal lobe pathology. *Id*.

Dr. Holmes conceded that, while it is possible that the varicella and pneumococcal vaccinations caused G.L.'s fever, he would not agree, and in fact believes it is "highly unlikely" that her fever or seizure was due to vaccination. Resp. Ex. C at 2. In his opinion, there is no evidence to support that G.L.'s vaccinations resulted in febrile seizures, or that febrile seizures resulted in frontal epilepsy. *Id*. at 3. He repeated that the association of febrile seizures with pneumococcal vaccine is very low and noted that subsequent immunizations with pneumococcal vaccine did not result in fever.[69] *Id*. at 2. "Neither Dr. Siegler or I feel there is any likelihood that the varicella vaccination resulted in a fever." *Id*. Dr. Holmes again suggested that G.L.'s high white blood cell count seen in the hospital after the first seizure indicated an infectious etiology for the

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[65] Jeremy M. Barry et al., *T2 Relaxation Time Post Febrile Status Epilepticus Predicts Cognitive Outcome*, 269 EXP. NEUROL. 242-52 (2015), filed as "Resp. Ex. C, Tab 32."

[66] Jeremy M. Barry et al., *Temporal Coordination of Hippocampal Neurons Reflects Cognitive Outcome Post-Febrile Status Epilepticus*, 7 EBIOMEDICINE 175-90 (2016), filed as "Resp. Ex. C, Tab 33."

[67] Katelin P. Patterson et al., *Enduring Memory Impairments Provoked by Developmental Febrile Seizures Are Mediated by Functional and Structural Effects of Neuronal Restrictive Silencing Factor*, 37 J. NEUROSCI. 3799-3812 (2017), filed as "Resp. Ex. C, Tab 35."

[68] Celine M. Dube et al., *Cognitive Dysfunction After Experimental Febrile Seizures*, 215 EXP. NEUROL. 167-77 (2009), filed as "Resp. Ex. C, Tab 34."

[69] Again, this is incorrect; G.L. did not have subsequent pneumococcal vaccinations, she received pneumococcal vaccinations on June 13, 2011; August 15, 2011; October 12, 2011; and April 16, 2012. *See* Pet. Ex. 2 at 1; Pet. Ex. 3 at 4. G.L. did not receive any additional pneumococcal vaccinations after April 16, 2012.

seizure. *Id*. Dr. Holmes then posited that the literature relied upon by Dr. Siegler to support his opinion that G.L.'s elevated white blood cell count was seizure-induced does not support that proposition. *Id*. Dr. Holmes submitted that G.L.'s blood work was evaluated due to infection, and though the evaluation was negative, viral etiology was not ruled out. *Id*.

Dr. Holmes submitted that G.L. had a focal left-sided seizure emanating from the right frontal lobe at the onset of her seizures. Resp. Ex. C at 1. Dr. Holmes attributed the seizures to a preexisting brain lesion. He submitted that, because of this lesion, her right frontal lobe was already prone to seizures which were simply triggered by her fever. *Id*.

He agreed that prolonged febrile seizures could result in damage to the hippocampus resulting in temporal lobe epilepsy but maintained that since G.L. did not sustain an injury to the temporal lobe during her febrile seizure, has a normal temporal lobe MRI, and does not have temporal lobe epilepsy; therefore, her epilepsy is not vaccine-related. Resp. Ex. C at 6-7. He also would not agree that G.L. experienced febrile status epilepticus. While Dr. Holmes agreed that G.L.'s first seizure occurred the day after her vaccinations and was a complex febrile seizure, he stated he is not clear on whether it was two separate seizures or one prolonged one. *Id*. at 2-3.

III. Legal Framework

The Vaccine Act provides two avenues for petitioners to receive compensation. First, a petitioner may demonstrate a "Table" injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the provided time period. § 11(c)(1)(C)(i). "In such a case, causation is presumed." *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *see* § 13(a)(1)(B). Second, where the alleged injury is not listed on the Vaccine Injury Table, a petitioner may demonstrate an "off-Table" injury, which requires that the petitioner "prove by a preponderance of the evidence that the vaccine at issue caused the injury." *Capizzano*, 440 F.3d at 1320; *see* § 11(c)(1)(C)(ii). A petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the alleged injury; showing that the vaccination was a "substantial factor" and a "but for" cause of the injury is sufficient for recovery. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999).[70] Once a petitioner has proven causation by preponderant evidence, "the burden then shifts to the respondent to show by a preponderance of the evidence that the injury is due to factors unrelated to the administration of the vaccine." *Deribeaux ex rel. Deribeaux v. Sec'y of Health & Human Servs.*, 717 F.3d 1363, 1367 (Fed. Cir. 2013) (citing § 13(a)(1)(B)).

The process for making factual determinations in Vaccine Program cases begins with analyzing the medical records, which are required to be filed with the petition. § 11(c)(2). Medical records created contemporaneously with the events they describe are presumed to be accurate and "complete" such that they present all relevant information on a patient's health problems. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). In making contemporaneous reports, "accuracy has an extra premium" given that the "proper treatment

[70] The Vaccine Act also requires petitioners to show by preponderant evidence that the "residual effects or complications" of the alleged vaccine-related injury lasted for more than six months. § 11(c)(1)(D)(i). It is undisputed that this six-month requirement is satisfied in this case.

hang[s] in the balance." *Id.* Contemporaneous medical records that are clear, consistent, and complete warrant substantial weight "as trustworthy evidence." *Id*. Indeed, "where later testimony conflicts with earlier contemporaneous documents, courts generally give the contemporaneous documentation more weight." *Campbell ex rel. Campbell v. Sec'y of Health & Human Servs.*, 69 Fed. Cl. 775, 779 (2006); *see United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1948). But petitioners can support their claim with oral testimony if it is credible and consistent with the medical records. *See, e.g., Stevenson ex rel. Stevenson v. Sec'y of Health & Human Servs.*, No. 90-2127V, 1994 WL 808592, at *7 (Fed. Cl. Spec. Mstr. June 27, 1994) (crediting the testimony of a fact witness whose "memory was sound" and "recollections were consistent with the other factual evidence"). In short, "the record as a whole" must be considered. § 13(a).

Furthermore, establishing a sound and reliable medical theory connecting the vaccine to the injury often requires a petitioner to present expert testimony in support of his or her claim. *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). The Supreme Court's opinion in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), requires that courts determine the reliability of an expert opinion before it may be considered as evidence. "In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." *Id*. at 590 (citation omitted). Thus, for Vaccine Act claims, a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly ex rel. Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010). The *Daubert* factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). And nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder ex rel. Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)).

Finally, although this decision discusses some but not all of the literature in detail, the undersigned reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty ex rel. Moriarty v. Sec'y of Health & Human Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision."); *Simanski v. Sec'y of Health & Human Servs.*, 115 Fed. Cl. 407, 436 (2014) ("[A] Special Master is 'not required to discuss every piece of evidence or testimony in her decision.'" (citation omitted)), *aff'd*, 601 F. App'x 982 (Fed. Cir. 2015).

IV. Analysis

Because petitioner does not allege an injury listed on the Vaccine Injury Table, their claim is classified as "off-Table." As noted above, for petitioner to prevail on an "off-Table" claim, he must show by preponderant evidence that G.L.'s injury resulted from the vaccinations at issue.

Capizzano, 440 F.3d at 1320. Doing so shifts the burden to respondent to show that the injury was caused by factors unrelated to the vaccinations. *Deribeaux*, 717 F.3d at 1367.

A. Petitioners' Burden to Show Causation

To prove causation, petitioner must satisfy the three-pronged test established in *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioner show by preponderant evidence that the vaccination B.L. received caused his injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278. Together, these prongs must show "that the vaccine was 'not only a but-for cause of the injury but also a substantial factor in bringing about the injury.'" *Stone v. Sec'y of Health & Human Servs.*, 676 F.3d 1373, 1379 (Fed. Cir. 2012) (quoting *Shyface*, 165 F.3d at 1352-53). Causation is determined on a case-by-case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Petitioner is not required to identify "specific biological mechanisms" to establish causation, nor are they required to present "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities." *Capizzano*, 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). "[C]lose calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280.

1. Reputable Medical Theory

The first *Althen* prong requires petitioner to provide a "reputable medical theory" demonstrating that the vaccines received *can* cause the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citation omitted). To satisfy this prong, petitioner's "theory of causation must be supported by a 'reputable medical or scientific explanation.'" *Andreu ex rel. Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1379 (Fed. Cir. 2009) (quoting *Althen*, 418 F.3d at 1278). This theory need only be "legally probable, not medically or scientifically certain." *Id.* at 1380 (emphasis omitted) (quoting *Knudsen*, 35 F.3d at 548). Nevertheless, "petitioners [must] proffer trustworthy testimony from experts who can find support for their theories in medical literature." *LaLonde v. Sec'y of Health & Human Servs.*, 746 F.3d 1334, 1341 (Fed. Cir. 2014).

Both Dr. Siegler and Dr. Holmes agreed that immunizations can result in fever that can trigger a febrile seizure. Tr. 100, 122. They agreed that febrile seizures can lower the seizure threshold, making a child more likely to suffer subsequent seizures. Tr. 66; Pet. Ex. 34 at 2; Resp. Ex. A at 11-12; Resp. Ex. C at 3. Furthermore, they agreed that complex seizures with all three features of complexity increases an individual's likelihood of developing epilepsy. Tr. 30, 106-08, 132-33; Pet. Ex. 15 at 2; Resp. Ex. A at 13.

Both experts agreed that prolonged febrile seizures may damage the developing brain. After this point, the experts differed. Dr. Holmes stated that, in a case of temporal lobe epilepsy, he would agree that the vaccine would have been the cause. Tr. 117-21, 122. However, he did not believe that there is any connection between prolonged complex febrile seizures, or febrile status epilepticus, and subsequent development of epilepsy in the frontal lobe. Tr. 135. He offered several

examples from medical literature of prolonged febrile seizures resulting in damage to the hippocampus and the temporal lobe but stated that he could not find any examples of prolonged febrile seizures resulting in damage to the frontal lobe. Tr. 135-36. Dr. Holmes' own submission of Verity noted that the risk of developing epilepsy was highest in children who had focal seizures and concluded that if febrile seizures caused brain damage that leads to later epilepsy, it is a rare occurrence. Resp. Ex. A, Tab 15 at 1; Tr. 86-87. However, Dr. Siegler offered medical literature showing that prolonged febrile seizures can lead to epilepsy in areas of the brain other than the temporal lobe, and, despite Dr. Holmes's opinion that the results of the study were not "statistically significant," *see* Resp. Ex. C at 4, I find that this literature provides the requisite support to Dr. Siegler's theory.

I am not bound by Dr. Holmes' preferences for statistical significance, and "a paucity of medical literature supporting a particular theory of causation cannot serve as a bar to recovery." *Andreu*, 569 F.3d at 1379 (citations omitted). While there may not be an overwhelming number of cases of frontal lobe epilepsy following prolonged febrile seizures, Dr. Siegler has offered literature to indicate that it can occur. "Unlikely" is not impossible, "less common" is not never, and thankfully, adverse reactions to vaccines are rare. However, they do occur. Both seizures and seizure disorders, including epilepsy, have been associated with the pneumococcal vaccine. *See, e.g., Graves v. Sec'y of Health & Human Servs*., 101 Fed. Cl. 310 (2011) (Finding seizure and death caused by pneumococcal vaccine where infant developed afebrile seizures within two days of receiving second pneumococcal vaccine); *Adams ex rel. Adams v. Sec'y of Health & Human Servs*., 76 Fed. Cl. 23, 41 (2007) (Finding seizure disorder caused by pneumococcal vaccine where infant developed febrile seizure within 24 hours of receiving third pneumococcal vaccine). Dr. Siegler has offered a sound and reliable medical theory that repeated prolonged complex febrile seizures reaching the level of febrile status epilepticus could cause brain damage resulting in frontal lobe epilepsy. Accordingly, I conclude that petitioner has satisfied prong I.

2. Logical Sequence of Cause and Effect and Proximate Temporal Relationship

The second *Althen* prong requires proof of a "logical sequence of cause and effect." *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1278). In other words, even if the vaccinations can cause the injury, petitioner must show "that it did so in [this] particular case." *Hodges v. Sec'y of Health & Human Servs.*, 9 F.3d 958, 962 n.4 (Fed. Cir. 1993) (citation omitted). "A reputable medical or scientific explanation must support this logical sequence of cause and effect," *id.* at 961 (citation omitted), and "treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury," *Paluck v. Sec'y of Health & Human Servs.*, 786 F.3d 1373, 1385 (Fed. Cir. 2015) (quoting *Andreu*, 569 F.3d at 1375). Petitioner is not, however, required "to eliminate alternative causes as part of establishing [their] prima facie case." *Doe v. Sec'y of Health & Human Servs.*, 601 F.3d 1349, 1357-58 (Fed. Cir. 2010); *see Walther v. Sec'y of Health & Human Servs.*, 485 F.3d 1146, 1152 (Fed. Cir. 2007) (holding that a "petitioner does not bear the burden of eliminating alternative independent potential causes").

To satisfy the third *Althen* prong, petitioner must establish a "proximate temporal relationship" between the vaccination and the alleged injury. *Althen*, 418 F.3d at 1281. This "requires preponderant proof that the onset of symptoms occurred within a timeframe for which,

given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan*, 539 F.3d at 1352. Typically, "a petitioner's failure to satisfy the proximate temporal relationship prong is due to the fact that onset was too late after the administration of a vaccine for the vaccine to be the cause." *Id.* However, "cases in which onset is too soon" also fail this prong; "in either case, the temporal relationship is not such that it is medically acceptable to conclude that the vaccination and the injury are causally linked." *Id.*; *see also Locane v. Sec'y of Health & Human Servs.*, 685 F.3d 1375, 1381 (Fed. Cir. 2012) ("[If] the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness.").

The resolution of prongs II and III in this case are simply best addressed together.

G.L had no history of seizures or neurological or cognitive deficits but was a normal healthy one-year-old child when she received her fourth pneumococcal and first varicella vaccinations on April 16, 2012. Within a day of receiving the subject vaccinations, G.L. developed a fever and had a seizure lasting longer than 25 minutes. Tr. 12; Pet. Ex. 2 at 4-5; Pet. Ex. 5 at 107. Although her white blood cell count was initially high, her doctors attributed it to the stress of her seizures, and it returned to normal the following day. No infection was found, nor was she treated for infection. Her treating physicians attributed the seizures to her vaccinations. Pet. Ex. 4 at 94; Pet. Ex. 5 at 123, 141. Two weeks later, she suffered another complex febrile seizure due to a viral infection, resulting in an episode of status epilepticus. Pet. Ex. 5 at 37. Several months later, G.L. received an MMR vaccination; within six days, she developed a fever and suffered another febrile complex seizure. Pet. Ex. 4 at 91. She ultimately developed afebrile complex seizures and intractable epilepsy.

Dr. Siegler opined that the vaccinations G.L. received on April 16, 2012, triggered her first febrile complex seizure, which in turn triggered a propensity for additional seizures due to neuronal hyperexcitability. Tr. 58. Dr. Siegler explained that this lowered G.L.'s seizure threshold, making her more susceptible to other environmental triggers of seizures, including febrile illness and vaccines. Tr. 58. She also had prolonged febrile seizures with three features of complexity, which placed her statistically at high risk for epilepsy. Tr. 58.

Dr. Holmes agreed that G.L. experienced a complex febrile seizure the day following her vaccinations but stated that it was unlikely the pneumococcal vaccine caused the seizure because epidemiological data indicates the risk of seizure following this vaccine is low. Tr. 90. "It can cause fever, so it's possible that the fever led to the febrile seizure. But there may be—it's not—it's certainly—I think it's unlikely the cause." Tr. 90. He went on to opine that G.L. had to have had an abnormality of the frontal lobe in order to have suffered a focal complex febrile seizure initially and to have developed frontal rather than temporal lobe epilepsy.

Both Dr. Siegler and Dr. Holmes are equally impressive and credible witnesses. However, while Dr. Holmes would not agree that G.L.'s vaccinations were in any way related to her febrile seizure or later development of epilepsy, he admitted that G.L. had no known neurological deficits prior to the subject vaccinations, and testing has not provided proof of a frontal lobe lesion or genetic cause. He also agreed that frontal lobe epilepsy is the most common epilepsy second to

temporal lobe epilepsy, and the literature supports the occasional development of extratemporal epilepsy following repetitive complex febrile seizures, though rare.

Here, G.L.'s treating physicians repeatedly attributed her initial febrile seizure to her receipt of the subject vaccinations. *See* Pet. Ex. 4 at 94; Pet. Ex. 5 at 123, 141. They performed extensive testing, including a nine-day EEG, but did not find evidence of a frontal lobe abnormality and, as of September 2017, have been unable to determine whether her epilepsy is focal or generalized. Pet. Ex. 11 at 57; Pet. Ex. 33 at 2. The Federal Circuit's direction in *Capizzano*, 440 F.3d at 1326, is for special masters to consider seriously the opinions of the vaccinee's treating doctors consistent with 42 U.S.C. § 300aa-13(b)(1)(A) and (B), directing the special masters to consider the entire record, including the diagnoses and medical judgments of doctors. Based on the opinions of G.L.'s treating physicians that her initial febrile seizure was triggered by her vaccinations and that she does not have a frontal lobe abnormality, coupled with Dr. Siegler's reports and testimony that prolonged febrile seizures with three features of complexity, like the ones suffered by G.L., can cause epilepsy, I find that G.L.'s pneumococcal and varicella vaccinations were a substantial factor in her development of complex febrile seizures within 24 hours of her vaccinations, and ultimately, intractable epilepsy.

There was no dispute that 24 hours was an appropriate time frame for the development of fever and seizures following the subject vaccines. Furthermore, Dr. Holmes agreed that fever six days after G.L.'s receipt of the MMR vaccine and development of seizures was also appropriate.

Petitioner has satisfied prongs II and III.

B. Burden Shifting: Respondent Must Show an Alternative Cause of Injury

A petitioner who satisfies all three prongs of the *Althen* test has established a prima facie showing of causation. *Hammitt v. Sec'y of Health & Human Servs*., 98 Fed. Cl. 719 (2011). Consequently, the burden now shifts to the government to prove that an alternative cause, unrelated to the administration of the vaccine, was the "sole substantial factor" in causing the alleged injury. *De Bazan*, 539 F.3d at 1354; *see also Hammitt*, 98 Fed. Cl. at 726 (explaining that respondent's burden is to show that the "factor unrelated" was the "sole substantial factor" in causing the injury). Additionally, a factor unrelated "may not include 'any idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness or condition.'" 42 U.S.C. § 300aa-13(a)(2); *see also Doe/11 v. Sec'y of Health & Human Servs.*, 83 Fed. Cl. 157 (2008) (holding that an idiopathic diagnosis cannot be a "factor unrelated," as it is idiopathic).

Respondent submitted two alternate causes of injury: first, that G.L.'s initial febrile seizure and later epilepsy was caused by a preexisting brain abnormality, and second, that G.L.'s initial febrile seizure was triggered by an infection rather than her vaccinations.

Dr. Holmes asserted that the G.L.'s elevated white blood cell count following her initial febrile seizure indicated an infection which caused her fever and complex febrile seizure. However, Dr. Holmes agreed that G.L.'s treating physicians tested her for infection, found no evidence of infection, did not treat her for infection, and ultimately attributed the elevation to her seizure activity. Moreover, G.L.'s white blood cell count was normal the following day without

any treatment. Despite this, Dr. Holmes continued to interpret G.L.'s high white blood cell count as indicative of a viral infection. I disagree. Based on the medical records and the opinions of G.L.'s treating physicians, I conclude that it is more likely than not that G.L. did not have an infection, viral or bacterial, but developed a fever as a result of the vaccines she received on April 16, 2012, and her high white blood cell count was a stress reaction to the complex febrile seizures that developed following the vaccinations.

Regarding the brain abnormality suggested by Dr. Holmes, there was no proof of any abnormality prior to G.L.'s complex febrile seizures and she did not develop epilepsy until almost two years after her seizures began, lending credence to Dr. Siegler's opinion that if G.L is said to have a functional lesion responsible for her frontal lobe epilepsy, it is the result of the severity and length of the repetitive seizures she suffered, not a preexisting condition. Additionally, when asked what G.L.'s brain abnormality was, Dr. Holmes stated that he could only speculate. Tr. 109. This does not convince me that G.L. had a preexisting brain abnormality when she was neurologically and cognitively normal prior to her first seizure, and no testing has shown evidence of a brain abnormality.

Based on the foregoing, I conclude that the pneumococcal conjugate and varicella vaccinations G.L. received on April 16, 2012, were the cause of or a substantial contributing factor in causing G.L.'s complex febrile seizures and subsequent development of intractable epilepsy two years later.

V. Conclusion

Petitioner has presented preponderant evidence that the pneumococcal conjugate and varicella vaccines G.L. received on April 16, 2012 were significant factors in her development of intractable epilepsy and has therefore demonstrated entitlement to compensation. This case shall proceed to damages.

IT IS SO ORDERED.

s/ Mindy Michaels Roth
Mindy Michaels Roth
Special Master